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THE MEDICAL CLINICS
OF
NORTH AMERICA

Volume 9 No 1

CLINIC OF DR WILLIAM ENGELBACH

MISSOURI BAPTIST SANITARIUM

STUDIES ON HAIR GROWTH AND PIGMENTATION

Dearth of Information on Pathogenesis of Abnormal Hair Growth and Pigmentation Contention that Body Hair Growth Is Normal Secondary Sex Characteristic Recent Research Relating Dermal Pigmentation and Growth of Hair to Pituitary and Suprarenal Glands Importance of Distribution and Character of Hair as Signs of Incretory Imbalance Vertex Alopecia Indicating Pituitarism; Marginal Alopecia, Hypothyroidism, General Hypotrichosis (Except Scalp), Hypogonadism; and Facial Hypertrichosis in Female, Cortical Suprarenal Disorder. Suprarenal Cortex Syndromes and Their Relation to Hair Growth and Pigmentation Vitiligo in Pituitarism and Scleroderma Association of Chloasma, Vitiligo, Hirsutism, and Virilism with Ductless Gland Disorders Abstracted Cases from Literature and Report of Personal Observations Results of Treatment

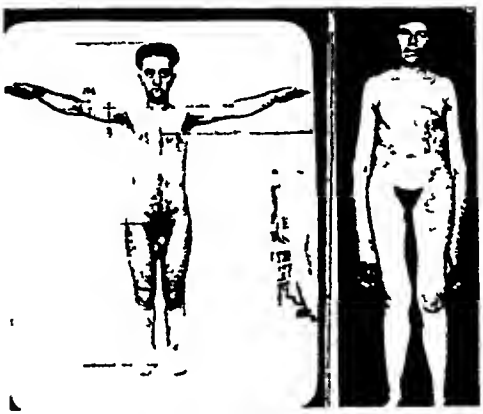
WITH the exception of Friedenthal's and Le Double's investigations there have been few serious etiologic studies concerning hair growth The dermatologic inquiries into this subject have been limited in most instances to localized skin lesions Much of the investigation as to these dermal lesions has been directed toward the histologic changes in the skin pigment and hair roots An inherent property influencing both the growth of hair and the deposition of pigment has been attributed to the individual

dermal cells If constitutional or distant conditions were considered the basic cause the attention was directed to infections focal or general, thought to exert an influence through the somatic nervous system Studies undertaken by the writer have encompassed a broader field, being directed toward the possible relationship of the internal secretions to these dermal changes These were initiated by repeated observations of marked abnormalities in hair growth and cutaneous pigmentation in positive incretory disorders

A recent interesting contribution relating to normal hair growth is that of Mildred Trotter Her studies have demonstrated that there is no difference in the sexes or races (white and negro) as to the abundance, length, and diameter of the facial hair until after the tenth year of age She asserts that after the tenth year of age the hair in males exceeds in length and diameter that in females and the facial hair of white women is somewhat more abundant and coarser than in the women of the negro race It has been assumed that the localized hair distribution following adolescence is a secondary sex characteristic The difference in the hair growth in the two sexes at adolescence, referable to awakened gonadial activity, has been difficult to explain For instance, hair appears at maturity on the mons and in the axillæ in both sexes but a long, thick growth on the face occurs only in the male An inherent property of the glandular hormones in each sex as to selective location of hair growth is probably the most logical explanation for the development of a male facial distribution following adolescence This same special hormonic predisposition is probably also productive of such differential sex characters as voice, stature, and mammary development This difference in facial hair growth in the sexes is possibly partially explained by Mildred Trotter's investigations, which demonstrate that the length and thickness of the hair, but not its abundance, have much to do with the apparent hairiness of this dermal surface

A well-known abnormality of hair growth is the state of *hypotrichosis* found present in the early castrate, eunuchoid, and thymicolymphatic types In these positive cases of *decreased*

gonadial function (Fig 1, B), this hypotrichosis is not universal, as the scalp is usually covered with a heavy growth of long, coarse hair It also has been accepted that *hypothyroidism* produces a tendency to *localized baldness* of the scalp and eyebrows In a vague sense hair growth has been connected with the function of the *suprarenal gland* because of the very marked *hirsutism* of *virilism*, supposedly a disorder of the cortex of this



A B

Fig 1 —A, Acromegaly, due to pituitary tumor, showing the characteristic hypertrichosis of the distal extremities and torso B, Eunuch castrated at the age of five, demonstrating a bodily hypotrichosis (taken from Falta and Meyers' Endocrine Diseases, 3d ed) Both are aged twenty-five Note the difference in proportions The former has a longer upper measurement than lower and a longer height than span the latter has a longer lower measurement than upper and a longer span than height In A these proportions are due to early fusion of the epiphyses of the long bones, with retention of the infantile dimensions, and in B, to very late epiphyseal closure, with resultant overgrowth of the long bones

gland The *increased growth of hair* in the large majority of positive cases of *pituitarism* (Fig 1, A), particularly on the distal extremities, in some instances on the chest and abdomen, has led to the belief that the hypophyseal hormones also influence the dermal appendages (as well as the osseous growth, genital function, etc)

There is even less known of dermal tissue pigmentation than of trichosis The well-known pigmentation of *Addison's disease*

(insufficiency of the medullary or chromaffin substance of the suprarenal gland) is demonstrative of the positive relationship of dermal discoloration to the endocrine system In the literature chloasma (melanoderma) has been ascribed to abnormal function of many organs It frequently has been designated as "liver spots," probably due to its yellowish tinge, and attributed to biliary function Its circumscribed location, however, is sufficient to distinguish it from biliary pigmentation Many of the older writers were inclined to believe that chloasma was due to ovarian disorder (chloasma uterinum) because of its association with menstrual disorders, such as amenorrhea and dysmenorrhea Knowing the interaction of the hypophysis and the generative organs, one can readily see how the ovaries might be suspected as its causation

Vitiligo and morphea (absence of pigmentation) have been attributed by dermatologists to lues more frequently than to any other disease or disorder The presence of *vitiligo* and *chloasma* in contiguous dermal areas occurring so often in pituitarism is conducive to the opinion that the *hypophysis* might also in some way produce a lack of normal pigment in the skin This heterodox state of a complete absence and an overproduction of pigment occurring in contiguous skin areas might be used as an argument against the theory that the dermal cells have an inherent power to store or cast off pigment under given conditions The disproportionate distribution of hair is another argument against the theory that a primary local cellular anomaly is responsible for either an unusual hairiness or a baldness of certain skin surfaces For example, an increased growth of coarse, thick hair on the distal extremities, existing with a tendency to increasing baldness at the vertex of the scalp, would speak against a local condition as responsible for either the cranial hypotrichosis or the extremital hypertrichosis On the other hand, the constant association of absence and abnormal deposition of pigment, and also of localized alopecia and hypertrichosis, with positive ductless gland disorders, could be interpreted as maintaining an incretory etiology for these various abnormal characters of the skin

Noteworthy contributions toward implicating the hypophysis as a factor in abnormal pigment deposit are those of P E Smith B M Allen, and W J Atwell Their conclusions from experimentation on tadpoles productive of changes in dermal pigment are as follows (1) That removal of the anterior lobe of the hypophysis in the frog tadpole will produce an amphibian very much lighter in color than its normal mates This type has been termed the "silvery" or "albino" tadpole (Fig 2)

Fig 2 —"Albino" or "silvery" (hypophysectomized) tadpole (from article by Wayne J Atwell, Endocrinology, vol 5, March, 1921) Contraction of the melanophores (darkly pigmented areas) and expansion of the xantholeukophores (light colored areas) result from this experiment

(2) That treatment of these "silvery" or "albino" tadpoles with extract of the posterior or the middle lobe of the bovine hypophysis causes a marked darkening of their surfaces due to change in their dermal pigment (3) Smith has produced these pigmentary changes in the "albino" tadpole with extracts of the posterior lobe, pars intermedia, and anterior lobe of the bovine hypophysis Atwell's experiments, however, did not result in a change of pigment from giving anterior lobe pituitary extract

except in very large amount, which would rapidly prove fatal to the tadpole Atwell ascribes the light color in the "silvery" or "albino" tadpole to the fact that the deeper melanophores are contracted and the epidermal melanophores and free epidermal melanin are reduced in amount following the removal of the anterior lobe of the hypophysis They assert that the "silvery" tadpole is light colored because of the contraction of the melanophores and lustrous because of the expansion of the light colored pigment cells, or xantholeukophores (4) McCord and Allen found that the normal frog tadpole is made much more transparent (called an "ashen" tadpole) by immersion in solution or emulsion of beef pineal substance in water Their study of the pigment cells in these tadpoles showed that the epidermal chromatophores were not perceptibly modified, but the deeper melanophores underwent very striking contractions The effect of the pineal substance was very transient, disappearing within a few hours unless the pineal matter was repeatedly added to the water Both Smith and Atwell confirmed most of the results obtained from these experiments with pineal gland They further noted that the xantholeukophores were not changed from their usual state of strong contraction

The tendency to a marked hide-hairiness, in which there is a diffuse growth of hair over the face (in the female) and the entire body, comparing to that normally found in the axillary and pubic regions in positive affections of the *suprarenal cortex* (confirmed at autopsy), has introduced this ductless glandular tissue as another factor influencing *hair growth* There also has been observed in some of these cases a brownish-black skin discoloration, which would suggest a disorder of this portion of the suprarenal as an etiologic influence in *abnormal dermal pigment*

Grouping —On this basis abnormal hair growth and pigmentation have been classified into two groups (1) *primary, related directly to disorder of the cortex of the suprarenal gland*, and (2) *secondary, associated with disorder of the hypophysis* It is suggested that probably the primary cause for hair growth, and possibly for pigmentation, will ultimately be proved to be in the suprarenal cortex If this is true, in pituitary cases having

abnormal dermal changes, these effects are produced by the action of the pituitary hormone upon the function of the suprarenal cortex This interaction of the pituitary gland and the suprarenal cortex is suspected not only from anomalies of hair growth and pigmentation in pituitary cases but also from the presence of osseous changes in positive suprarenal cortex disorders similar to those found in acromegaly (See Case X, Fig 24 A B, Fig 25, C, D)

Delille, Fischer, and Fischer and Schultze have reported cases of acromegaly in which there was noted a hyperplasia of the suprarenal Fischer and Schultze noted the entire suprarenal cortex, as well as medulla, hyperplastic, while Delille observed a hyperplasia only of the cortex The hypertrichosis in acromegaly is assumed to be secondary, possibly related to the suprarenal cortex through the hormonic action of these two glands The parts of the glands operating in this procedure (as designated) are the anterior lobe of the hypophysis and the cortex of the suprarenal Unfortunately, the hormones from these endocrine structures are not sufficiently elaborated to allow of further deductions than those drawn mainly from clinical investigation

It is interesting in considering these two endocrine glands (suprarenal and hypophysis) associated clinically with abnormal over- or underproduction of hair and pigment to note their similarity embryologically, histologically, and physiologically They are dualistic glands, having two separate and distinct portions derived from different embryologic sources The suprarenal medulla is derived from the ectoderm and the cortex from the mesoderm (the wolffian duct, a part of the sexual system) The anterior lobe of the hypophysis is derived from the epithelial portion of Rathke's pouch, the posterior lobe from the diencephalon Histologically, the anterior pituitary lobe and the cortex of the suprarenal are the cellular portions of the glands, whereas the posterior lobe of the hypophysis and the medulla of the suprarenal consist entirely of neural tissue Physiologically the two portions of each gland have entirely different functions Epinephrin (from the suprarenal medulla) and the

extract from the posterior pituitary lobe may be considered positive hormones, both having specific effects upon involuntary muscle contraction Evans and his collaborators have recently demonstrated characteristic effects upon growth, estrum, and ovulation from extracts of the anterior lobe of the pituitary when injected into the peritoneum of rats The active principle of the suprarenal cortex (if such there is) has not been isolated However, clinical cases showing positive cortex lesions at postmortem have demonstrated that the function of this glandular tissue also must be related to growth and to genital function and development, as well as influential in dermal changes The interrelation of the anterior lobe of the hypophysis and the suprarenal cortex has been shown in experimental work on animals, in which the removal of one of these organs produces demonstrable changes in the other Clinically, their interrelation has been shown by the effects upon common hormonic signs, such as the osseous and genital, as well as by the trichosis and pigmentation found so frequently in disorders of both of these endocrine structures

The *distribution of hair growth* is as important a diagnostic sign of ductless gland disorder as is the distribution of panniculus in endocrine adiposity It is well known, for instance, that a supraclavicular and a dorsal hand and foot padding indicate a hypothyroidism, a classical girdle obesity, a hypopituitarism, and a mammary and mons panniculus, a hypogonadism (1) The fact that there is so constant an association of a disproportionate *overgrowth of hair on the distal extremities* with a partial or final complete *vertex alopecia* (Figs 3, A, 3, B, and 5, B) in *acromegaly* or an acromegalic type of individual is significant This frequent combination of hyper- and hypotrichosis in the acromegalic would indicate that a cranial alopecia in the non-pathogenic pituitary type of individual might also be referred to the function of the hypophyseal gland This alopecia begins at the frontotemporal angle, with a gradual recession of the hairline along the temporal ridge, until finally the entire vertex of the head is bald, with a residual growth along the lateral or marginal scalp (2) *Hypothyroid* baldness begins along the margin of the scalp (*marginal alopecia*), oftenest along the

temporal regions, less frequently at the occiput rarely, unless in a terminal complete involvement, extending to the vertex (Figs 4, A, 4, B, and 5, A) The character of the new growth

A B

Fig 3 —Beginning vertex alopecia in positive pituitary disorder of both sexes Note the extension of the baldness toward the vertex at the frontotemporal angles A (Case III) is aged eighteen, B, aged forty

A B

Fig 4 —Marginal alopecia due to hypothyroidism in the adult (A) and in childhood (B) Note the normal growth on the vertex, with tendency to baldness at the margins of the scalp The former reacted completely to thyroid therapy

of hair in these two conditions (vertex and marginal alopecia) differs Thyroidism produces a very marked change in the gross character of the hair The new hair is usually of a very delicate, fine quality as compared with that previous to the onset of the

condition (3) The *hypotrichosis* of *hypogonadism* (Fig 1, B) as present in early castrates, eunuchoids, and status thymicolymphaticus is one affecting the body *but not the scalp* which is usually fully covered with long coarse hair This condition contrasts sharply with the vertex alopecia and hypertrichosis of the distal extremities and body so often present in acromegaly (4) *Virilism* supposed to be due to disorder of the *suprarenal cortex*, has as a sign a *generalized hypertrichosis* (Figs 28–31) involving both the body and face That on the body is of the intensity of hide-harness, being coarse and long as that

A B

Fig 5 —Comparison of marginal (hypothyroid) and vertex (pituitary) alopecia in the preadult age A, Hypothyroid girl with a typical marginal alopecia almost completely encircling the scalp B, Positive pituitarism, aged thirty-one, with a characteristic vertex alopecia

ordinarily present in the axillæ and on the mons The special characteristic of this condition, however is the marked facial hair, particularly in the female, effecting a full growth of mustache and beard (5) Just the opposite of this generalized hypertrichosis is a *universal hypotrichosis* (Fig 6) a falling out of the hair and failure of recurrent growth, involving the scalp, eyebrows eyelids axillæ, and mons In some of these cases studied by the writer there has been evidence of an insufficiency of a number of ductless glands However, whether this glandular affection had any relation to the absence of hair is questionable Two illustrative cases are as follows

Case I Generalized Hypotrichosis —Miss F R , No 3611, aged thirty-four (Figs 6–8) The patient gave a history of attacks of localized alopecia for twenty-five years A generalized atrichia of scalp and body had been present for a year pre-

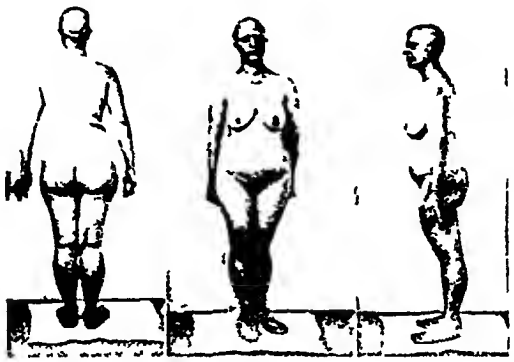
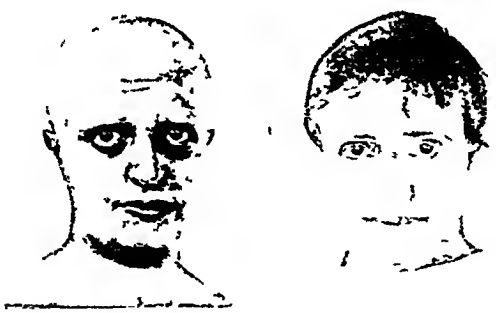


Fig 6 —Complete hypotrichosis (scalp, brows, axillæ mons and body surfaces) in a pluriglandular disorder (Case I)



A B

Fig 7 —Same case as Fig 6, before (A) and after (B) substitution thyroid and pituitary treatment

ceding observation At the age of ten a bald spot ½ inch in diameter appeared above the left ear and two or three years later other bald spots occurred Her head was shaved at that time and within one year the hair grew over the entire scalp

At seventeen another bald spot appeared, and at twenty-three the hair of the entire scalp began falling out with a coincident thinning of the axillary and pubic hair Local treatment, the patient stated, produced a complete cure, the hair of the scalp regaining its normal thickness and quality At twenty-nine the condition recurred and one year before observation the hair from the scalp, eyebrows, eyelids, axillæ, mons, and other dermal surfaces had entirely disappeared During this year she had undergone continuous local treatment, as well as constitutional, including thyroid medication, without the slightest sign of a return of hair growth A medical survey was made, with a

A B

Fig 8—Scalp of Case I (same as Figs 6 and 7) before (A) and after (B) treatment

diagnosis of *alopecia* due to an *early hypothyroidism*, probably changed to a *thyropituitary insufficiency* The only abnormal signs besides the thyroid developmental history and pituitary make-up, osseous and orthodontial changes were a hypotension (blood-pressure, 90/60) and a decreased sugar tolerance, without glycosuria She was placed under therapy consisting of thyroid and pituitary substances by mouth and extract of anterior lobe pituitary intramuscularly Six months after treatment was begun hair appeared on the scalp, eyebrows, eyelids, and in the axillæ Eight months later she had almost complete restoration of the entire dermal hair growth (Figs 7, 8)

from knees to dorsal feet (Fig 11) In some cases, however, the chest and abdomen are also covered with a thick growth of hair This same disproportionate hair distribution is noted in many individuals of pituitary make-up who do not have pathologic signs of acromegaly For instance, the short, stocky individual having the upper measurement (symphysis to vertex) longer than the lower (symphysis to soles of feet) and an unusual growth of hair on the distal extremities not infrequently has either a complete or a partial vertex alopecia The writer first became interested in the possible relationship of the vertex alopecias to pituitarism from a study of hypophyseal cases in both sexes ranging from fourteen to nineteen years of age The following are illustrative cases

Case III —Mr C F, No 2567, aged eighteen (Fig 3, A) This patient had a beginning vertex alopecia, the marginal scalp being well supplied with coarse, thickly distributed hair There were positive signs of pituitarism (osseous, orthodontial, and genital) He had been under the observation of a very competent dermatologist, and prolonged thyroid gland and local dermatologic treatment produced no change in the alopecia The thyroid treatment was given also under our observation for more than six months and during this time there was noted a progressive retraction of the hairline, with a thinning of the vertex hair He was then placed under pituitary treatment, anterior lobe substance by mouth and hypodermically This was followed by a vertex growth practically as thick as at the margins of the scalp Following withdrawal of this treatment, a relapse occurred, characterized by a continued progression of the alopecia

Case IV —Miss O K, No 1554, aged nineteen Since the age of thirteen there had been a gradual thinning of the hair, particularly at the vertex and the frontotemporal margins The marginal hair otherwise was practically normal in distribution, length, and quality The patient had taken special scalp and local dermatologic treatment and thyroid gland substance

Fig 10.—Acromegaly (from Falta and Meyers' Endocrine Diseases) Note the hypertrichosis of the distal extremities, with a coexistent vertex alopecia

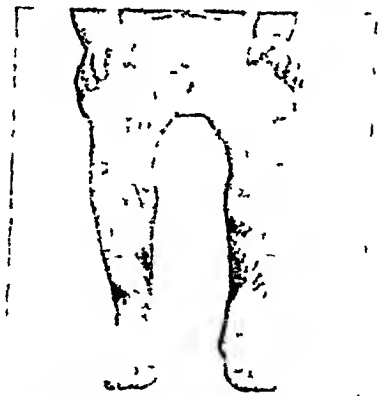


Fig 11.—Positive case of pituitary tumor with hypertrichosis of the distal extremities

pictures of acromegaly (*Fig 10*) one is impressed with the frequency in this condition of this disproportionate hair growth and distribution The hypertrichosis is located most characteristically on the distal extremities, from elbows to fingers and

from knees to dorsal feet (Fig 11) In some cases, however, the chest and abdomen are also covered with a thick growth of hair This same disproportionate hair distribution is noted in many individuals of pituitary make-up who do not have pathologic signs of acromegaly For instance, the short, stocky individual having the upper measurement (symphysis to vertex) longer than the lower (symphysis to soles of feet) and an unusual growth of hair on the distal extremities not infrequently has either a complete or a partial vertex alopecia The writer first became interested in the possible relationship of the vertex alopecias to pituitarism from a study of hypophyseal cases in both sexes ranging from fourteen to nineteen years of age The following are illustrative cases

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internally without arresting the progress of this alopecia On pituitary treatment (desiccated anterior lobe substance by mouth and extract of this lobe hypodermically) for a number of months, there was no further progression No marked increase in length or abundance of the hair occurred, although there appeared a slight growth of new hair

A number of months' treatment in these cases, however, is insufficient for basing an opinion of ultimate results The treatment should not be discontinued, through discouragement, for at least one year Sometimes after an interval of continuously increasing baldness, a final complete normal growth is accomplished It should be stated that the relationship to endocrine treatment of this renewed growth of hair in these cases has not been definitely established

Pigmentation —The experimental work of Smith and Atwell on tadpoles with relation to the hypophysis, in which they produced decrease in and restoration of pigmentation, has its clinical bearing in the interpretation of the pigmentation found in pituitary disorders in the human In the pure insufficiency of the anterior lobe of the hypophysis (as demonstrated in the Loram-Levi type) without posterior lobe disorder, as well as in the bilobar (Frohlich's) syndrome, vitiligo and chloasma, varying in intensity and distribution, are among the constant signs (as shown in Fig 12)

Case V Bilobar Hypopituitarism [1]—Mrs R D J, No 2384, aged twenty-four (Fig 12) This is a classical case, presenting the syndrome of an enormous gain in weight (100 pounds within one year, following a gradual increase of 50 pounds from the age of maturity), a complete amenorrhea for one year, associated symptoms of headache, hot flushes, nausea and vomiting, rapid decay of the teeth and pigmentation Substitution of both lobes of the pituitary gland by mouth and hypodermically resulted in the return of her menses for two months For the following year the patient failed to receive treatment and during this time

[1] Reported in Tice's *Practice of Medicine*, vol viii, 1921 (W F Prior Co, Hagerstown, Md)

her menses recurred regularly, but were very scanty, less than one day in duration There were no changes in her obesity, pigmentation or other hormonic signs during this short course of treatment or the year following

Fig 12 —Extensive chloasma and coincident vitiligo of the neck and arms in a bilobar hypopituitarism (Case V)

The following case is also one of chloasmas associated with positive pituitary disorder and illustrates the hereditary tendency in endocrine dysfunction

Case VI —A young woman having a very classical pituitary syndrome applied for medical opinion regarding an amenorrhea, with a coincident dysmenorrhea occurring at intervals of five to eight months In addition to the pituitary signs of obesity, osseous and orthodontial changes, and amenorrhea, she had a very prominent chloasma and contiguous vitiligo Her mother also had a very marked chloasma and vitiligo of the hands (as shown in Fig 13) Inquiry concerning the mother's menstrual history revealed that she had had long intervals of amenorrhea, with intermittent metrorrhagia and dysmenorrhea, and from her general type (short stocky, and obese) one would suspect a

bilobar hypopituitarism No other family history of amenorrhea, obesity, or dermal pigmentation, to the patient's knowledge, could be elicited

Fig 13 —Chloasma and vitiligo of the hands *(referred to under Case VI)*

A B

Fig 14 —Pituitary insufficiency showing (A) a beginning vertex alopecia and (B) a marked chloasma and vitiligo of the arms

An interesting case presenting a combination of vertex alopecia with vitiligo and chloasma is shown in Fig 14 This chloasma pigmentation is rarer and is less marked and extensive

in the male than in the female Figure 15 demonstrates a very positive pigmentation about the forehead and face in a classical male acromegalic type

Case VII —Mr G W , No 2407, aged thirty-one (Fig 15) This patient presented himself for a hypersexuality He had the positive signs of acromegaly, as evidenced in the *x*-ray of the osseous system, orthodontial changes, pigmentation, etc He was a member of a religious order which required celibacy He

Fig 15 —Chloasma of the forehead and face in a positive acromegalic (Case VII)

was unusually conscientious in the work of his order and had risen to a high standing due to his mental ability Notwithstanding his religious faith, philosophy, and the extreme discipline of this order, his inability to control his sexual impulses finally forced him to resign

The above case demonstrates the effect of endocrine hyperactivity upon the sexuality, in turn influencing the conduct of the individual

In association with the unusual deposition of pigment, or chloasma, in many positive pituitary disorders, as has been

stated, there has been noted the absence of dermal pigment (vitiligo) Vitiligo frequently exists side by side with an overdevelopment of pigment in localized skin areas, the contrast being sufficient to allow its photographic reproduction (Fig 12) The chloasma in pituitary disorders is located about the hairline of the forehead, angles of the mouth, jaw, nipples, and in other tissues which are the seats of pigmentation, as verrucæ Variation in the intensity of this pigment has been observed, particularly in females during the menses and pregnancy Variation has also been noted in cases in which there is favorable therapeutic response in the general signs of pituitarism, as decrease in obesity, return of the menstrual flow in amenorrheal cases, etc This is considered additional reason for crediting the changes of dermal pigmentation in these cases to the function of the anterior lobe of the hypophysis Chloasma is particularly important in a nulliparous woman, owing to its physiologic occurrence in the primipara and the fact that it often becomes permanent after once established, being intensified by various conditions Erdheim and Stumme have noted the constant physiologic enlargement of the hypophysis during pregnancy In the pituitary type of woman other mild hypophyseal signs are noted during pregnancy A subdermal infiltration about the short and flat bones of the face and extremities (producing a thickening of these overlying tissues) and blunting of the peaked bones are sometimes present in pregnancy and considered a pituitary sign Therefore, in a woman who has conceived, chloasma may be due to a physiologic hyperactivity of the hypophysis occurring during the previous pregnancy and need not be related to abnormal function of this gland in the succeeding years It is well known that many cases of acromegaly begin with and are a continuation of physiologic changes in pregnancy The following case (Fig 16) is an illustration of the etiologic influence of pregnancy in acromegaly

Case VIII —Mrs C F , No 3486, aged thirty-two (Fig 16) The patient entered the hospital in good condition for delivery She had developed outspoken signs of pituitarism during her

pregnancy, consisting of a very marked chloasma, with intensification of the pigment in the verrucæ, an abnormal growth of hair about the arms and face, blunting of the peaked bones, and enlargement of the hands and feet Following her delivery, instead of subsiding (as after normal pregnancy), these conditions progressed Her hands and feet continued to enlarge, the hair growth on the arms and below the knees increased, and the pigmentation about the face, neck, and in the verrucæ was intensified She developed into a very classical case of acromegaly

Fig 16—Acromegaly following pregnancy (Case VIII) Note the marked hypertrichosis of the arms and face, with the increased pigmentation of the verrucæ. The typical "spade" hand and the normal hand are shown in comparison

The presence of vitiligo in these positive pituitary disorders (Fig 17) has led to a further study of conditions, such as scleroderma, having vitiligo as one of the frequent dermal changes The effect of extract of the posterior lobe pituitary gland upon the vascularity of the skin (as evidenced by its production of pallor, from constriction of the dermal arterioles, described by the writer as a "vascular reaction") has directed the attention to the pituitary treatment of scleroderma A number of cases of scleroderma were treated with extract of the posterior lobe of the hypophysis in order to determine any marked effect upon the

Fig 17 —Cloasma and vitiligo in positive pituitary disorders.

vitiliginous areas or the general contraction of the skin from such therapy In the more advanced cases in which the sclerodermal

areas were very large comparatively little effect of treatment was noted In some of the cases of morphea or small localized areas of scleroderma, a very marked change occurred following the institution of pituitary treatment

Case IX —Miss M K , No 3246, aged four (Fig 18, A and B) Referred by Drs Mook and Engman

The patient had a localized scleroderma in the right anterior cervical region, which was progressing by pseudopod extension upward along the folds of the neck to the region behind the ear

A B

Fig 18 —Morphea, or localized scleroderma, before (A) and after (B) pituitary treatment (Case IX)

and over the crest of the lower maxilla For eight months after the onset this progression was continuous although dermatologic treatment, consisting of local applications, x-ray and ultraviolet rays, and internal medication of thyroid gland had been administered constantly Following our first observation of the case thyroid therapy was continued for two months, during which time the lesion progressed The treatment was then changed to pituitary substance, entire gland, 15 to 20 grains (1–1 3 gm) daily by mouth and obstetric pituitrin 10 minims (o 6 c c) intramuscularly weekly A marked effect was noted

in the sclerodermal areas, first manifested by a change from a pearly white aspect to a pinkish tinge, indicating a return of vascularization in this area Apparently a new growth of blood-vessels caused the white, contracted, fixed area gradually to revert to a normal skin tissue which could not be differentiated from the surrounding skin

Primary (Suprarenal Cortex) Hypertrichosis and Pigmentation—As stated in our previous gross grouping of these cases, until more definite proof excluding the *suprarenal* as the primary cause of these abnormal skin characters is presented, this gland will be considered the most probable endocrine tissue directly

Fig 19 Fig 20 Fig 21

Fig 19—Facial hypertrichosis in a bilobar hypophyseal insufficiency with an amenorrhea of three years Note the separation of the upper teeth

Fig 20—Facial trichosis in a pituitary (bilobar) insufficiency

Fig 21—Facial hirsutism occurring with a suprarenal cortex tumor

responsible for these specific dermal changes It is now well established that the medullary portion of the suprarenal gland can be excluded as an etiologic factor in chloasma, vitiligo, or hypertrichosis The pigmentation of Addison's disease is of an entirely different character and distribution It is a diffuse dirty yellow discoloration or impregnation of the skin and present in somewhat circumscribed form on the visible mucous membrane of the conjunctiva, mouth, and rectum The *hypertrichosis* related to suprarenal cortex disorder is different in location and distribution from a secondary or pituitary hair

[illegible] The facial hir- [illegible] it occurs in [illegible] conditions which [illegible] often is so [illegible] and mustache [illegible] In these cases however, it is [illegible] owing to [illegible] this blemishing con- [illegible] electrolysis and [illegible] effectively The hair on the remainder of the body is soft, coarse and thickly distributed but it sometimes produces a picture of hide-hairiness as intense as the normal axillary or pubic hair

Disorders of the Suprarenal Cortex.—The suprarenal cortex [illegible] when classical are becoming clearly enough defined to be considered positive clinical syndromes Yet there has not been sufficient control in these cases to warrant a positive diagnosis of abnormal activity of the suprarenal cortex without physical evidence of tumor involving the upper pole of the kidney or the suprarenal gland However, studies referable to the relationship of the suprarenal cortical substance to these dermal changes can be carried out as advantageously clinically as experimentally The symptom complexes vary considerably with the age at which the cortical disorder occurs For this reason they can be most conveniently grouped as follows I Preadolescent type II. Postadolescent type III Those associated with markedly abnormal anatomic development of the genital system, as in hermaphroditism (Figs 22, 27)

I The preadolescent type have the following cardinal signs (1) *Precocious, premature physical development, with retention of the infantile dimensions* (2) *Advanced osseous development*, evidenced by the *early appearance and fusion of the epiphyseal nuclei* (3) *Marked advance in development of the primary and secondary sex characters* (4) *Retardation of the*

psyche and sex instinct disproportionate to the physical and genital development (5) *Hypertrichosis* (6) *Adiposity* These last two are present in only a certain percentage The accelerated ossification, which can be determined by the proper roentgenograms for the developmental age, while a very important diagnostic sign, is merely that present with every hypergenitalism in the juvenile age It would not differentiate this condition from a hyperpinealism producing a macrogenitosomia,

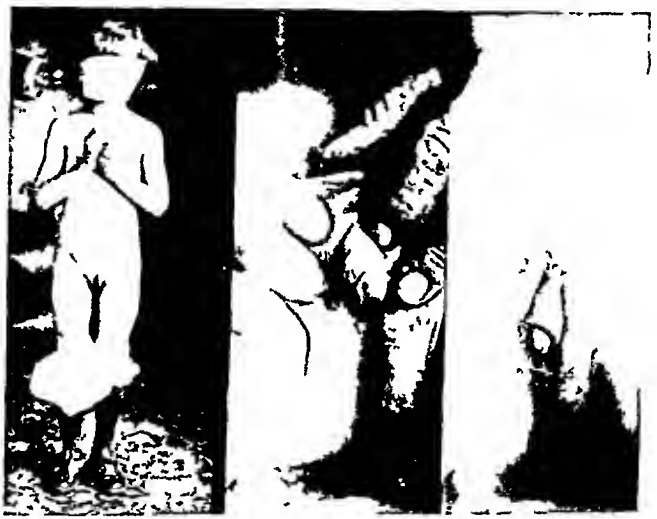
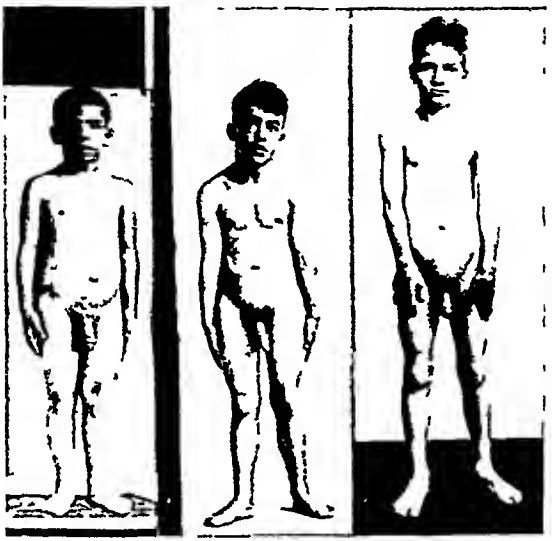


Fig 22 —Case of pseudohermaphroditism (by courtesy of Dr Jas H Hutton, Chicago) Note the hypotrichosis, which probably debars this case from classification with the suprarenal cortex disorders

also characterized by increased size and function of the generative organs Hypertrichosis and adiposity rarely occur with the latter type of pubertas præcox (Fig 23) The adiposity is not a common complement of all preadolescent suprarenal cortex cases, being present in about 30 per cent. of those collected from the literature Hypertrichosis is much less frequent in this type than in the postadolescent variety The majority of preadolescent cases reported to date are female, and probably less than half of these had a facial hair growth The literature on

this subject has been reviewed by Neurath and Glynn Of 17 cases collected by Glynn, 14 were of the female sex Individual reports of positive cases controlled by autopsy in females ranging in age from four months to eleven years have been made by Cooke, Tilesius, Ogle, Calcott-Fox, Orth, Dobbertin, Bullock and Sequeira, and others, and in males from one-half year to



A B C

Fig 23 —Cases of microgenitosomia (probably due to pinealism) Note the absence of hypertrichosis, which helps to differentiate the precocious genital and physical development in these cases from suprarenal cortex disorder (Figure C, on the right, published through the courtesy of Dr Wm McKim Marriott, Children's Hospital, St Louis, shown in comparison with two of the writer's cases)

fourteen and one-half years, by Linser and Adams A summary of a few of these positive cases follows[1]

Case of Glynn Girl five years old This patient was as large as a normal fourteen-year-old girl Hair was present on the upper lip, pubis, and back The sex organs were especially

[1] From Falta and Meyers' Endocrine Diseases, 3d ed , P Blakiston's Son & Company, Philadelphia

well developed Obesity was present At autopsy a large tumor of the suprarenal cortex was found The ovaries and hypophysis were normal

Case of Linser Boy five and one-half years old His general appearance was that of a youth, for which reason he was admitted to the men's department of the hospital He was 138 cm in height The penis was 8 to 9 cm long, the testicles were as large as a pigeon's egg, and the prostate was like that of a fifteen-year-old boy The size of the body, ossification of the epiphyseal ends, and teeth corresponded to those of a fifteen-year-old boy The upper measurement was longer than the lower Adiposity was present Autopsy showed tumor of the suprarenal cortex The hypophysis was normal

Case of Richards Girl seven years old At the age of five she developed pubic and facial hair At seven years she looked like a woman twenty years old

Case of French Girl seven years old, having an abnormal hair growth, which had begun to develop at the age of eighteen months The genital organs were very large Autopsy revealed a suprarenal tumor

Case of Jump, Beates, and Babcock Girl seven years old, showing a precocious development of the external genitalia, with an enlarged clitoris An unusual growth of pubic hair was present The menses had not appeared The patient died during an operation for removal of the hypernephroma

Case of Bullock and Sequeira Girl eleven years old The general development was that of a forty-year-old woman Her height was 4 feet, 6 inches, her weight, 87 pounds Menstruation had begun at the age of nine and three-fourths years The breasts were fully developed and long hairs were present on the genitalia Adiposity had developed and had increased with the age Autopsy showed a large tumor of the left suprarenal, with metastases, hyperplasia of the thyroid and parathyroids, a fully developed uterus, and large ovaries, with corpora lutea of recent date

Case of Adams Boy fourteen and three-fourths years of age Puberty began at the age of ten The boy was unusually

large and muscular The autopsy showed a tumor of the left suprarenal cortex

II The postadolescent variety of disorder of the suprarenal cortex present the following associated signs (1) *Hypertrichosis*, noted particularly in the female, in whom there appears a mustache and facial hair growth, as well as a marked overgrowth of the hair on the body, involving the posterior thorax, the abdomen, and the extremities (2) *Inversion of the physical type* toward that of the opposite sex, with wide pelvis and genu valgum in the male and narrow, elliptic pelvis and genu varum in the female (3) *Genital dysfunction*, evidenced by increased or decreased sexuality, such as nymphomania, frigidity, and amenorrhea in the female and excessive libido and potency or impotency in the male These changes in the female are often associated with a deepening of the voice, in character and tone resembling that of the male (4) *Adiposity*, consisting of a generalized deposition, not conforming to the other endocrine types of obesity (present in less than 50 per cent of the cases) (5) A *circumscribed black or brown pigment* of the face and bodily folds (as the axillary, inguinal, and at the elbows and knees) The hypertrichosis in postadolescent cases is probably the most constant objective sign In the female it is especially suggestive of suprarenal cortex lesion or disorder There are nearly always associated with it genital dysfunction and inversion of the sex type Pigmentation and adiposity may or may not be present in individual cases Their absence does not discredit the diagnosis

An abstracted review of a few of the cases in the literature is given, demonstrating the prevalence of facial hypertrichosis in postadolescent cases

Case of Bortz and Thumin Female aged sixteen and three-fourths years, with abnormally rapid development a few years after adolescence Amenorrhea occurred within one year after adolescence, coincidentally with a *luxuriant hair growth*, consisting of a *black beard and mustache* and an unusual growth of hair *over the chest and linea alba* The voice became deeper and a universal adiposity developed Autopsy revealed bilateral

tumor of the suprarenal gland, atrophic ovaries, and an enormously enlarged thyroid gland The hypophysis was normal

Case of Winkler Girl sixteen years old She had an abundant *growth of black hair on the upper lip* The uterus was small Autopsy showed a tumor of the right suprarenal, with metastases

Case of Launois, Pinard, and Gallais Girl nineteen years old The menses began at the age of thirteen At seventeen violent vomiting, with severe abdominal pain, occurred Obesity, which finally became colossal, and mental changes developed Amenorrhea also occurred, accompanied by emaciation, and finally a *general hypertrichosis*, with a *black beard and mustache* A tumor of the right suprarenal was found at postmortem

Case of Bovin Female twenty-eight years old Amenorrhea occurred at twenty-one The patient had had two normal pregnancies previously to this age At the time of the amenorrhea an *overgrowth of the hair on the abdomen* and a *beard* appeared Simultaneously there developed an abdominal tumor Operation revealed a large ovarian tumor having its origin in embryonal rests of the suprarenal tissue The patient recovered from the operation, *after which the uterus enlarged, the menses reappeared, and the abnormal hair growth disappeared*

Case of Dalaché Female aged twenty-eight, with a *beard and mustache* Amenorrhea occurred following abortion

Case of Goldschwend Female aged thirty-nine, who had had 5 children before the age of thirty-six The menses stopped at thirty-six This was coincident with the development of an abdominal tumor Accompanying the amenorrhea and abdominal tumor, there was a *marked hypertrichosis* about the body, particularly the abdomen, and a *mustache and beard* Autopsy revealed a malignant adenoma of the left suprarenal The uterus and ovaries were small The epiphysis and hypophysis were normal

Case of Santi Female fifty-three years of age, who had had two normal pregnancies before the age of forty-seven The menses had been regular until forty-seven, when they became more frequent until there was an almost constant menstrual flow Enlargement of the abdomen occurred coincidentally

with an enormous obesity Autopsy showed a tumor of the kidney proceeding from separated suprarenal germs and a similar tumor of the ovary There was no statement as to hair growth

III. The group of disorders of the cortical substance of the suprarenal having a greater or less marked tendency to hermaphroditism were thoroughly reviewed by v Neugebauer, who collected 13 positive cases of suprarenal tumor These cases are medical curiosities and so rare that they need no great consideration Marchand, Engelhardt, Fiebiger, Hepner and Ogston, and Meixner report cases in the adult and newborn The adult cases had the classical suprarenal hair distribution, involving the face and entire body, whereas some of the cases reported before the adolescent age were free from hypertrichosis

As illustrative of the suspect syndrome of suprarenal cortex disorder, the following personally observed cases are abstracted (Figs 24–29, 31)

Case X —Miss E Y , No 4084, aged eighteen (Figs 24–27) The menses of this patient appeared first at the age of thirteen and were very irregular, with intervals of two to three months The flow was two or three days in duration, moderate in amount, without dysmenorrheal symptoms These imperfect periods continued until the age of fourteen, when the patient had an attack of rheumatism, following which the menses ceased entirely, and until the age of eighteen, when the observations were made, a complete amenorrhea existed Coincident with the cessation of her periods there was noted a tendency to *overgrowth of the hair on the face and body* Soon afterward a deep brownish-black pigmentation appeared about the axillæ, skin folds of the body, chin, lower maxilla, and median anterior cervical region (Fig 25, C and D) About a year following the amenorrhea, hypertrichosis, and pigmentation, her mother noted very decided changes in her features, which had been rather sharply angled (Fig 24, A) The nose, chin, and other peaked bones began to show distinct blunting (Figs 24, B 25, C and D) The skin and subdermal tissue of the face became thickened

so as to give her a sullen drowsy appearance An infiltration about the wrists and hands, feet and ankles was also observed Her configuration was of the male type, with narrow pelvis and absence of the genu valgum (Fig 26, E) The only other abnormal physical sign was a markedly enlarged clitoris (Fig 27), presenting a tendency to pseudohermaphroditism No

A B

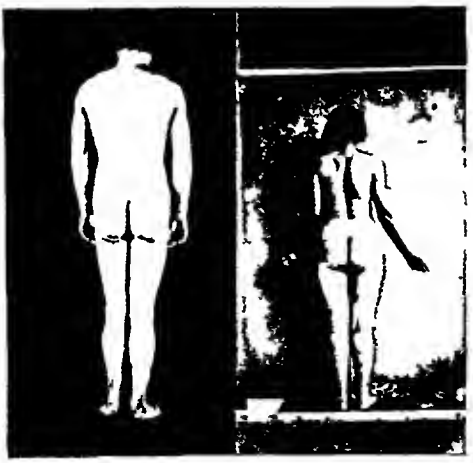
Fig 24—Suprarenal cortex disorder (Case X), aged fifteen (A) and eighteen (B), before and after evidence of cortical suprarenal disorder occurred Note the difference in facial contour In A the features are sharply angled, in B the nose and chin are blunt and a marked subdermal infiltration of the face is present

physical or pyelographic evidence of an enlargement of the suprarenal or encroachment upon the pelvis of the kidney was found

She was placed under various endocrine therapy for four months without the production of any perceptible change in her syndrome By permission of the patient the right suprarenal gland was then explored by Dr F W Bailey, without

C D

Fig 25.—Same case as Fig 24, A and B (suprarenal cortex disorder, Case X) Note the blunting of the facial peaked bones, the brownish-black pigmentation about the axillæ and chin and the unusual muscular development



E F

Fig 26.—E is the posterior view of Case X (same as Figs 24, 25), illustrating the tendency to the opposite sex stature Note the narrow pelvis, genu varum, and unusual muscular development F is Case XII, also a suprarenal cortex disorder

finding any abnormality in consistency or macroscopic appearance On the day following the operation, the patient for the first time within four years had an apparently normal menstrual flow, which continued for one and one-half days There was also at that time an almost complete disappearance of the brownish-black pigmentation about the lower chin and axillæ Whether this menstrual flow was a coincidence or in any way related to the exploration of the suprarenal gland is undeter-

Fig 27 —Case X Note the enlarged clitoris, showing a tendency to pseudohermaphroditism

mined The patient returned to her home in Tacoma, Washington, and has reported since that she has had no further recurrence of her menstrual flow and that her pigmentation has returned as marked as ever

Case XI.—Miss A S, No 4225, aged twenty (Fig 28) The chief complaints of this patient were loss of interest in all activities, extreme timidity and reserve, irregular menses, a gain in weight from 94 to 185 pounds within two years, and somnolence Until adolescence (at the age of thirteen) she had been a very bright, active child, leading her classes at school having a host of friends, and entering into all social activities of a girl of her age With the onset of her menstruation, she began

to change very decidedly mentally She lost all initiative and failed to recognize any responsibility At times, without apparent cause, she would not speak to her mother or brother for several days She preferred being alone, not leaving her home except to receive facial treatments for removal of the facial hair Her psychic stigmata increased and she finally began to speak of herself as inferior socially to other people

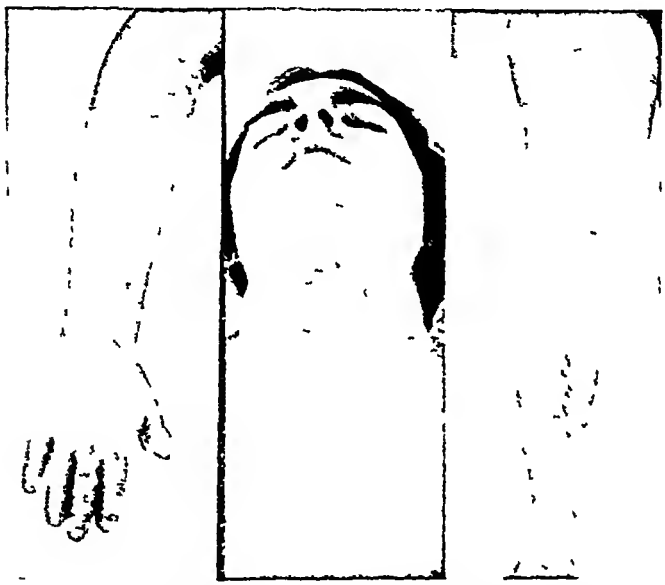


Fig 28 —Suprarenal cortex disorder (Case XI) Hypertrichosis of the arms, legs, and face (The facial hair had been largely removed by depilatory treatment)

Her menses were always irregular, with intervals of four to six weeks, seven to fourteen days in duration, moderate in amount and without dysmenorrhea Following a change from Arkansas to Wisconsin to attend the university, the patient had an amenorrhea of eighteen months The periods recurred when she returned home, but remained irregular At the time of the prolonged amenorrhea, she began to gain weight, increasing during the following two years from 94 to 185 pounds During

the six months preceding observation, the weight decreased to 155 pounds Somnolence had been a symptom for several years, the amount of sleep averaging fifteen hours daily

The physical examination revealed a type tending toward the male, with facial and general hypertrichosis, narrow pelvis, genu varum, and overdevelopment of the clitoris and labia majora The hirsutism was characterized by long hair on the lower extremities, a masculine distribution on the abdomen, a localization on the upper posterior thorax, from the cervical region down over the lumbosacral, and a facial growth involving the cheeks, upper lip, rami of the mandible, and submental region

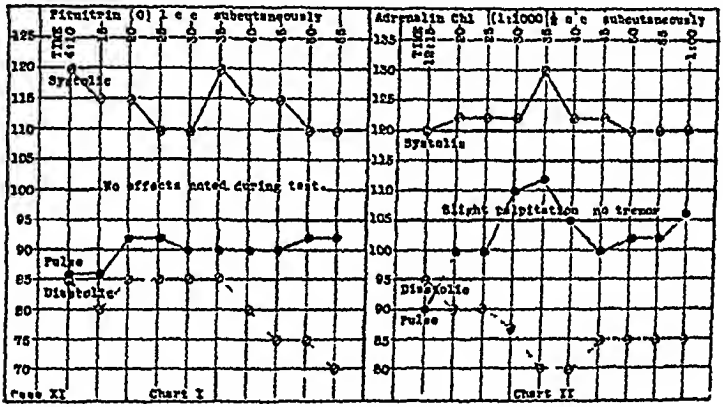


Fig 29 (Case XI)

The adrenalin test was positive, the pituitrin test, negative (Fig 29) A complete medical survey, with these exceptions, revealed no abnormalities

Case XII.—Miss N F , No 3375, aged seventeen (Fig 26, F) The patient was referred for examination by the St Louis Psychiatric Clinic because of a voluntary delinquency of three years She had been adopted at the age of five into surroundings of refinement and culture and evidently had been unable to adjust herself to her environment, which was of the most liberal and agreeable She would leave home for a number of nights at a time, seeking company in lower levels of society Her

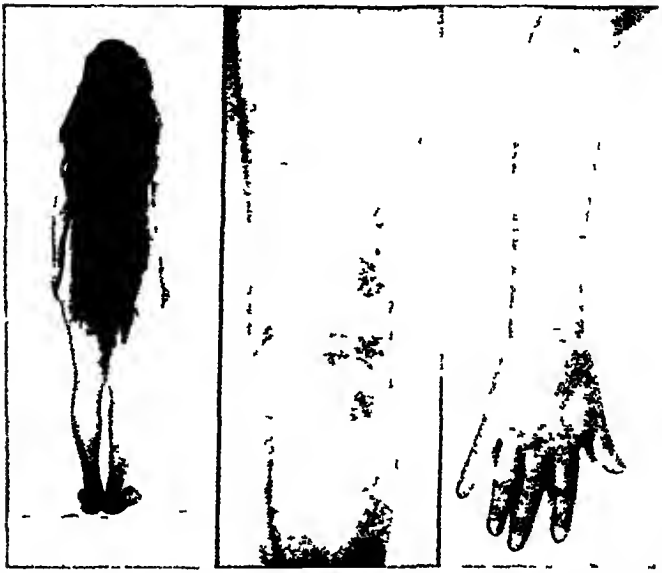


Fig 30 —Suprarenal cortex disorder Note the hypertrichosis of the scalp, legs, and arms

Fig 31 —Hypertrichosis existing with a bilobar pituitary insufficiency

intellectual development was adjudged normal by a psychiatrist, although she was given to fabrication and deception

The menses began at fifteen and were irregular, with intermissions of two or three months, until the sixteenth year During that year they were regular, with intervals of twenty-eight days, moderate in amount, four days in duration, and accompanied by no abnormal symptoms A hypertrichosis about the extremities and posterior thorax developed at that time She also had an unusual growth in stature during the eight months preceding observation, following her sixteenth birthday

The basal metabolic rate was −15 per cent, the blood-pressure, 100 (systolic), and the adrenalin response negative

This case does not present the quadrisymptom complex required for a suprarenal cortex disorder, yet the generalized hypertrichosis and menstrual disturbance without other determinable cause would suggest this condition very strongly

Case XIII.—Mr A J P, No 4320, aged twenty-six (Fig 32) The patient had masturbated since the age of fourteen and for four or five years previous to the age of twenty-three (three years before observation) had performed this act almost daily At that time he made a number of unsuccessful attempts at sexual intercourse Subsequently he gradually lost his potency At the time of observation a complete absence of potency and libido had existed for one year He had had nocturnal emissions, without erection, every three or four nights (occasionally twice a night) for the preceding three years A marked fatigability had been present for two years Nervousness was one of the chief symptoms, characterized by excitability, irritability, marked oppression, and decreased memory and concentration He was given to worrying over trifles and to introspection with regard to his condition Other symptoms were increased perspiration and occasional throbbing headaches of one day's duration The nervousness and depression had become so extreme that he would shut himself in completely, refusing to associate with any one except as required by his daily professional duties

Physical examination revealed an excessive hypertrichosis involving the thorax, loins, and extremities, and a recent tendency to vertex alopecia A suspect diagnosis of *primary hyperactivity of the cortex of the suprarenal, recently changed into insufficiency* of this glandular tissue, was made in this case. The hyperfunction of this gland produced a very marked hypersexuality, which was finally changed to a hyposexuality The

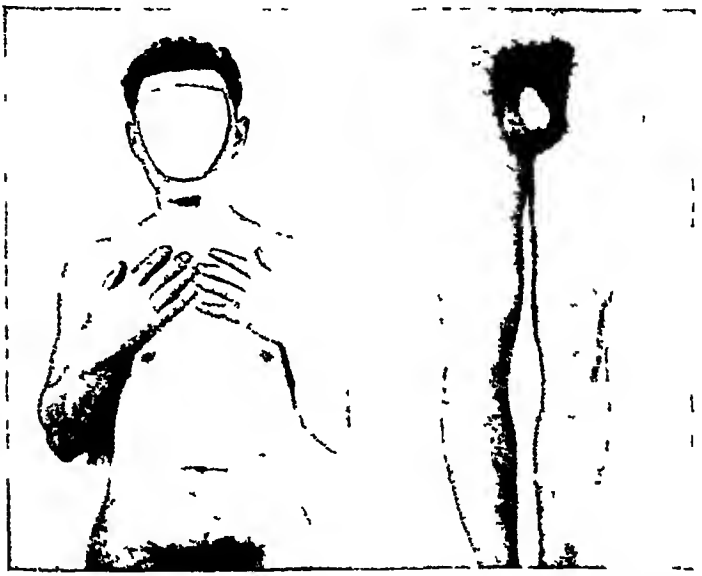


Fig 32 —Suprarenal cortex disorder (Case XIII) The chief symptom was a complete loss of potency at the age of twenty-five Note the marked hypertrichosis on the legs (The hair of the arms and torso is not well depicted in this photograph)

marked hypertrichosis and associated abnormal genital function would arouse these suspicions There also might be secondarily a possible disturbance of function of the anterior lobe pituitary gland, from the tendency to vertex alopecia so often present in the acromegalic type having a hypertrichosis The unusual body hair growth is much more pronounced than that associated with pituitarism and in itself would lead one to suspect cortical lesion of the adrenal as accounting for the entire symptomatology

Pathology.—The positive cases of suprarenal cortex disorder have at autopsy nearly all shown signs of a hypernephroma of the cortex. The tumors are made up of round or oval polygonal cells of epithelial character having many shapes. They retain much of their embryologic character, probably due to the fact that the suprarenal cortex originates from the mesoderm. For this reason, they appear to be histologically primary sarcoma. Woolley differentiates them from suprarenal sarcoma by the fact that they do not have true lumina. The benign form of adenoma or so-called Grawitz tumor, may originate from embryonal suprarenal rests in the kidney, ovary, or tail of the pancreas. Clinically, it is significant that these Grawitz tumors are never associated with alterations in the function of the suprarenal cortex as evidenced by changes in the somatic or genital sphere. This was recently brought out by Stoerck and Zehbe. They sometimes do become large enough to produce pressure symptoms and frequently metastases. Westphal collected 24 of these adenomata from the literature and added 7 from his own statistics. In 2 of his cases he reported a glycosuria.

Bittorf reported 2 cases of *unilateral hypernephroma* having a general picture of Addison's disease. *Both were cured by operation*, all symptoms being relieved except the pigmentation. This fact that Addison's disease might be due to unilateral suprarenal medullary insufficiency should be kept in mind, for, as illustrated by these 2 cases, the fatal prognosis in Addison's disease might be averted in the small percentage of cases having this unilateral involvement.

While it is true that nearly all the positive cases in the literature thus far have been related definitely to tumefaction of the cortex of the suprarenal or of embryonal suprarenal rests in the ovary, testis, or pancreas, a few have shown at postmortem a simple hyperplasia, or unilateral or bilateral swelling, of the suprarenal cortex. Most of these positive cases of simple hyperplasia will be found classified with the pseudohermaphroditisms, having all the signs of a suprarenal cortex complex and living to an old age. This is the basis for the hypothesis that many of these cases (particularly of the younger ages) having a duration

of a number of years are probably associated with a functional cortical lesion of the suprarenal, without definite structural changes in the cortex or the surrounding tissue, as the medulla, kidney, or other contiguous organs

The study of trichosis and pigmentation from an endocrinologic viewpoint leads one into an unexplored field, which yet demands a very considerable investigation and confirmation While it is true that the internal secretions afford an explanation for some types of hair growth and pigmentation, it is likely that there are etiologic factors bearing upon these dermal changes which are entirely independent of the endocrine and autonomic nervous systems One can but feel that clinical combined with other investigative work directed toward solving the physiologic functions of these endocrine tissues which influence the dermal structures will be rewarded by significant discoveries The advancements in this study, too, should have a wider application than those pertaining merely to treatment of these facial and other disfigurements, as they would open the field for a better conception of the hormonic effects of these glands as related to the development and function of other systems Owing to our imperfect knowledge of the physiology of the suprarenal cortex, therapy directed toward the relief of conditions with which it is related has been of little avail In the dermal conditions associated with pituitarism the treatment has been effective only in those cases in which the general endocrine states have been remediable It is hoped, however, that a continuation of these studies will stimulate research which will supply the key to the pathogenesis of these aberrant dermal states This, in turn, will introduce a physiologic interpretation which will be the means of a more rational therapy

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CLINIC OF DR McKIM MARRIOTT

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HYDROCEPHALUS

THE spinal fluid is secreted, in greater part at least, by the choroid plexuses in the cerebral ventricles Little, if any, of this fluid is absorbed in the ventricles, but passes out through the aqueduct of Sylvius and the foramina of Luschka and Magendie to the subarachnoid spaces over the surface of the brain and surrounding the spinal cord Absorption of the fluid occurs chiefly in the subarachnoid space Under ordinary conditions a perfect balance is maintained between secretion and absorption The spinal fluid fills the ventricles and the subarachnoid spaces, but remains under a low pressure If for any reason the balance between secretion and absorption is disturbed so that an excess of spinal fluid accumulates, hydrostatic pressure will rise and will cause compression of the brain and ultimately lead to enlargement of the cranial cavity

Inasmuch as the fluid is chiefly secreted in the ventricles, and is absorbed in the subarachnoid spaces, the pressure of the fluid will be greater in the ventricles than elsewhere The hydrocephalus is, therefore, usually of the "internal" variety, *i e*, there is an excess accumulation and excess pressure of spinal fluid in the ventricles of the brain The effect of this is the distention, especially of the lateral ventricles, which results in compression atrophy of the brain and a progressive increase in the size of the head

Hydrocephalus may exist as a congenital condition, or may be acquired at any time during life Congenital hydrocephalus is often the result of blocking of the passages by which the spinal

fluid passes from the ventricles to the subarachnoid space In other instances there is a disturbance of the balance between secretion and absorption so that an increased accumulation of fluid results, even though the passages remain open In some of these patients fluids seem to be excreted in excessive amounts In others absorption from the subarachnoid is poor There is a close relationship between congenital hydrocephalus and spina bifida It is probable that an excess production of spinal fluid in intra-uterine life is one of the important causes of spina bifida The fluid in the subarachnoid being under increased pressure the spinal meninges bulge out, and in this way prevent closure of the spinal canal In other cases the spinal canal closes but the head enlarges In the case of many patients with spina bifida removal of the sac and closure of the opening results in the prompt development of hydrocephalus

Acquired hydrocephalus is the result of any condition which leads to an increased secretion of spinal fluid or to a blocking of the paths of absorption In any form of meningitis more or less inflammatory exudate is poured out and mixes with the spinal fluid, thus increasing its volume Absorption may not be increased sufficiently to care for this excess of fluid In some forms of meningitis there is also likely to be a blocking off of a portion of the subarachnoid space or damage to the vessels and lymphatics which are concerned with absorption Some degree of hydrocephalus is common during the acute stages of any type of meningitis In a certain number of instances the damage due to inflammation is such that there is complete blocking of the foramina or firm adhesions which render inactive a portion of the subarachnoid spaces In these cases the hydrocephalus is progressive Brain tumors particularly those located in the region of the cerebellum or pons may, by pressure, close off the passages through which the fluid reaches the subarachnoid spaces and this will, of course, lead to a distention of the ventricles with fluid

The diagnosis of hydrocephalus, especially if it is well marked, offers very little difficulty The increased size and progressive enlargement of the head, out of proportion to the rest of the body, the characteristic bulging of the forehead, and in the

case of infants, the wide-open bulging fontanels the visual disturbances, the characteristic rolling down of the eyes, the peculiar percussion note given when the skull is tapped, all point to the existence of the condition But the diagnosis of the particular type of hydrocephalus is somewhat more difficult and is of considerable importance, if intelligent treatment is to be pursued The treatment will depend upon the cause and nature of the condition and may in a considerable number of instances be entirely successful

Not so many years ago hydrocephalus was considered incurable but at the present time methods are available by which a certain number of patients may be successfully treated Whatever form of treatment is adopted it should be instituted early, inasmuch as a severe degree of hydrocephalus leads to marked mental deterioration, a mild degree of hydrocephalus however, is quite compatible with normal and even superior mentality

The cases selected for presentation today illustrate some of common types of hydrocephalus and the methods of diagnosis and treatment which should be adopted

Case I.—This infant is now four months of age She was born at term and seemed to be normal except for a spina bifida Over the fourth and fifth lumbar vertebræ there was a protruding sac about the size of half a lemon covered by a thin almost transparent membrane normal skin extended only up to the edge of the sac. The head was said to be of approximately normal size and shape at the time of birth The mother noticed, however that the head grew rapidly following birth. The infant was brought to the hospital at the age of three weeks and at this time the evidences of hydrocephalus were unmistakable The anterior and posterior fontanels and the sagittal sutures were wide open and bulging the forehead was prominent. the maximum circumference of the head was 2 inches greater than the average for normal infants of the same age. Pressure on the head caused the lumbar sac to swell. There was therefore obviously free communication between the ventricles and the spinal subarachnoid. A lumbar puncture was not done. There

was some spasticity of both legs The physical examination was otherwise negative The infant was well nourished and took all feedings well The cry was lusty Blood Wassermann was negative, and tuberculin skin test was negative It was evident that this was a case of congenital hydrocephalus due in all likelihood to a production of spinal fluid in excess of absorption

The spina bifida was considered inoperable by Dr Ernest Sachs, and on his recommendation the sac was subjected to dry heat, a method of treatment which has been found to be satisfactory in such cases A frame containing electric lights was put over the child's bed and the sac baked in this way As a result of this treatment the sac shriveled up considerably and finally scarred fairly well, as can be seen The head, however, increased rapidly in size The increase in circumference during the first week in the hospital was at the rate of approximately $\frac{1}{2}$ inch a day, whereas the normal rate of growth at this age is about $\frac{1}{2}$ inch a month

In a case of this type it is advisable to first attempt medical means of treatment The most successful of these means in our experience is the administration of theobromin-sodio-salicylate (diuretin) The rationale of this method of treatment has been discussed elsewhere [1]

This patient was given 0 05 gm ($\frac{3}{4}$ gr) of diuretin by mouth three times a day, for a period of one week During this time the head increased in size about $\frac{1}{4}$ inch The dosage of diuretin was then increased to 0 15 gm ($2\frac{1}{2}$ gr) three times a day This was kept up for a week and a half and during that time the increase in the size of the head was $\frac{1}{8}$ inch The dosage of diuretin was then increased to 0 2 gm (3 gr) three times a day and the size of the head remained constant The diuretin was then stopped for a period of three days in order to determine whether or not the cessation of growth seemed to be definitely related to the giving of the diuretin The head increased $\frac{3}{4}$ inch in circumference

[1] The Use of Theobromine Sodio Salicylate (Diuretin) in the Treatment of Hydrocephalus, McKim Marriott, Amer Jour Dis Child, October, 1924, vol 28, p 479

during these three days The diuretin administration was resumed in the dosage of 0 2 gm (3 gr) three times a day and under this treatment the circumference of the head has continued to remain stationary

Although the hydrocephalus seems to have been arrested, this infant is not doing well Pyelocystitis, which is a frequent complication of spina bifida, has developed and the ultimate prognosis is not good The treatment with diuretin should be continued In such a case one may hope that if the infant survives and grows that a balance between secretion and absorption of spinal fluid may be attained and that further treatment can be dispensed with If not, such surgical procedures as removal of the choroid plexus from one or both ventricles, as recommended by Dandy, should be considered, or subcutaneous drainage, as recommended by Sachs

Case II —The second patient is fifteen months of age and was entirely normal during the first three months of life At the age of three months the infant developed high fever and had numerous convulsions The head was retracted and the back arched These symptoms persisted for some time There was no physician in attendance and no lumbar puncture was done at that time The mother stated that following this attack the child's head had been getting rapidly larger Two months after this, when the child was five months of age, she was brought to the St. Louis Children's Hospital At that time there was evident hydrocephalus The head was about $1\frac{3}{4}$ inches larger in circumference than that of an average infant of the same age A lumbar puncture was done and a large amount of clear fluid removed The fluid was under increased pressure and pressure on the wide open fontanel caused fluid to spurt from the lumbar puncture needle The fluid was clear and contained 5 cells per cubic millimeter The Wassermann reaction was negative on blood and spinal fluid, and the tuberculin skin test was also negative The child was undernourished, but seemed fairly intelligent There was some spasticity of the legs

From the history of this case it appeared probable that the

tion between the ventricles and the spinal subarachnoid spaces The fluid contained 3 cells, no globulin, and the Wassermann reaction was negative There was therefore no question of an active meningitis

In such a case treatment with diuretin is likely to be unsuccessful, inasmuch as there is no chance for absorption of fluid Surgical procedures offer the only hope of successful treatment Operation was performed by Dr Ernest Sachs The fourth ventricle and basal cisterna were exposed and it was found that the cisterna was completely obliterated and that the aqueduct of Sylvius was not patent The cerebellum was lifted and a small rubber catheter inserted so as to open the channel of the aqueduct and in this way a free flow of cerebrospinal fluid was obtained The catheter was allowed to remain in for several days and was then removed Shortly afterward the operative wound was completely closed It is now seventeen months since the operation was performed and the head is exactly the same size as it was at the time of the operation The patient is developing well in a physical way, can talk some, but is unable to raise its head In this case the further progress of the hydrocephalus has been arrested, but, unfortunately, serious damage had occurred before treatment was instituted

The particular surgical operation to be recommended in cases of hydrocephalus depends upon the nature of the process If there is an operable tumor present which is causing obstruction the tumor is, of course, removed In other cases of obstruction of the aqueduct of Sylvius puncture of the corpus callosum, so as to allow passage of the spinal fluid from the ventricle out to the subarachnoid spaces has been successful Complete removal of the choroid plexus from one or both ventricles has been advocated by Dandy and satisfactory results have been obtained in a few instances The mortality of this operation, however, is high

Another procedure, and one which has been successful in several of our patients, is the operation recommended by Sachs, in which the roof of the fourth ventricle is removed and the spinal fluid allowed to drain subcutaneously

Case IV —The next case illustrates a different type of hydrocephalus and one for which a distinctly different form of treatment must be adopted This patient is eight months of age and was brought to the hospital with the complaint of a large head and repeated convulsions The infant was apparently normal at birth and was breast fed, but never gained weight in a normal manner It was noticed by the mother that the head had been enlarging ever since the first few weeks of life. At the age of five months the child had a number of convulsions, but otherwise there were no acute illnesses The child was first brought to the hospital at the age of five and a half months She was much undernourished and the head was distinctly enlarged The fontanels, both anterior and posterior, were open and bulging The sagittal suture was not closed Physical examination otherwise was negative A lumbar puncture was done The fluid was clear and flowed freely The fluid contained 60 cells per cubic centimeter, which were almost entirely monoculears The fluid gave a positive globulin test. The colloidal gold reaction was 0001121000, a definitely abnormal finding The Wassermann reaction on the blood and spinal fluid was 4+ in all antigens

This was obviously a case of congenital syphilis in which the meninges were involved The hydrocephalus was the result of a syphilitic meningitis

It has been shown that in approximately one-third of the cases of congenital syphilis some involvement of the central nervous system is present, but only rarely is there sufficient meningeal involvement to lead to the condition of hydrocephalus

The indication for treatment is clear in a case of this type The patient was given the usual treatment for congenital syphilis, *i e*, three intravenous injections of arsphenamin were given at weekly intervals The dose was 0 01 gm for each kilogram of body weight At the same time the infant was given intramuscular injections of 1 per cent. mercuric chlorid solution in an amount of 0 05 c.c. ($\frac{1}{2}$ min) per kilogram of body weight weekly Besides this 1/5 gr of mercury with chalk was given three times daily by mouth

It is usually not advisable to give any intraspinous treatment until the general treatment has been administered for some time because of the fact that serious reactions occasionally occur which have been interpreted as being due to a sudden killing off of spirochetes in the central nervous system

In this particular case at the end of one month of general treatment the patient was given a Swift-Ellis intraspinous treatment, *i e*, the mother of the patient received a full dose of arsphenamin and one-half hour later a small quantity of blood was removed from the mother and allowed to clot The serum was separated, inactivated, and 8 c c of this serum given to the baby intraspinously This same treatment has been repeated once since

The infant has received altogether three courses of three doses each of arsphenamin intravenously, and mercury injections have been kept up At the present time the infant is in good general condition, has gained weight well with simple feeding, has had no further convulsions and the head, although larger than normal, is not increasing in size The Wassermann reaction on the blood and spinal fluid is now negative This patient should nevertheless continue to receive antisyphilitic treatment for at least another year It will be unnecessary to resort to any further procedures in so far as the hydrocephalus is concerned

This group of cases illustrates very well the general methods of procedure which are to be adopted in handling a case of hydrocephalus The first step is to determine whether or not the hydrocephalus is the result of an active meningitis or if it is due to obstruction between the ventricles and subarachnoid spaces Information regarding the first point can be obtained from an examination of the cerebrospinal fluid The fluid obtained by lumbar puncture may be clear, whereas that obtained from the ventricles may contain an excess of cells or may even be definitely purulent Both ventricular and lumbar puncture should usually be done This is easily accomplished in the case of infants Information as to communication between the ventricles and the subarachnoid spaces is obtained by observing whether or not there is a free flow of fluid on lumbar puncture

and if the fluids in the ventricles and in the subarachnoid spaces are under the same degree of pressure, further, whether pressure on the fontanel causes a distinct increase in the flow of fluid from the lumbar puncture needle

In the case of active meningitis due to the meningococcus appropriate serum treatment should be instituted, and it is well to note in this connection that in the case of infants with meningococcus meningitis it is advantageous to administer serum into the ventricles as well as into the spinal subarachnoid space In syphilitic meningitis appropriate antisyphilitic treatment should be instituted In the so-called "acute hydrocephalus" of tuberculous meningitis treatment is at best palliative and should consist in frequent lumbar punctures

When the hydrocephalus is of the "communicating' type *i e*, when there is free communication between the ventricles and the subarachnoid diuretin should be administered, and usually this treatment leads to good results When the hydrocephalus is of the non-communicative type surgical procedures are indicated

and the like Acquired mental deficiency is the type seen as the result of some infection as meningitis or encephalitis or the mental retardation which at times develops in the course of epilepsy

Perhaps as satisfactory a classification as any is a simple grouping according to the anatomic or pathologic type presented These are

1 Simple amentia The majority of cases belong to this group which is made up of all cases not falling into one of the following groups Most of these types are self-explanatory and I do not consider it worth while to discuss each type in detail, as they are fully covered in nearly every text-book on pediatrics

2 Microcephalus

3 Hydrocephalus

4 Mongolism

5 Cretinism (Most important from the standpoint of therapy)

6 Amaurotic family idiocy

7 Deficiency accompanying spastic birth palsies as a result of hemorrhage

8 Acquired deficiency as a result of

(*a*) Congenital syphilis

(*b*) Meningitis or encephalitis

(*c*) Epilepsy

Regardless of the type or cause of mental deficiency, the most useful and important one from a practical standpoint is a classification or grouping based upon the degree of deficiency or retardation It is difficult to apply this classification in considering infants, but for children over three years it is most important, as the ultimate disposition of the mentally deficient individual must be based upon the degree of retardation For many years a classification into (1) idiots, mental development under two years' level, (2) imbeciles, mental development two to seven years, (3) morons, mental development seven to ten years, has been in use While satisfactory in a gross way from the viewpoint of medical classification, modern psychology has developed a much more accurate method of determining the mental age

From a practical standpoint the classification ... ever be used, as the terms "idiot" and "imbecile" ... sense of horror and despair to the parents ... without accomplishing any definite purpose ... child as "retarded" with a mental age of one ... the case may be, adequately covers the ... standpoint

Diagnosis.—The diagnosis of mental defect ... infant may be easy or difficult in the individual ... baby presents some of the marked disturbances ... deficiency as hydrocephalus, microcephalus ... spastic paralysis, an obviously low grade of mental ... is often evident. As we have pointed out, however, ... of patients with mental deficiency belong in the ... amentia, and in these there may be no gross ... development of the brain or mental powers ... has to be guided more by what the baby fails ... any striking positive evidence.

In the first two years of life the evidence ... more of a physical nature than of a purely mental ... rule, the average baby does certain things with ... regularity which more or less denote normal progress. ... head is held up steadily at four months and ... time the infant usually grasps quite definitely ... is particularly true of the nursing bottle, if the baby is ... fed. At about six or seven months the baby ... very definite recognition of the mother or nurse ... close attendance. At about nine months the ... without support. Walking is more irregular, but ... baby will make a definite attempt to walk by ... month. Speech is even more irregular in its ... ment, but, as a rule, single words will be used ... twelve month and from six to twelve months ... be put together in short but complete sentences. ... that a baby is free from obvious physical defects, ... malnutrition, failure to follow the above progress ... suspicious of mental deficiency. Thus failure ...

up at five months or to grasp at objects by the sixth or seventh month, or failure to sit up alone by the twelfth month, while not in themselves evidence of mental deficiency, should always suggest such a possibility to the mind of the physician who should watch the progress of the baby more closely without alarming the parents Walking may be delayed and is perhaps the least important of the items In the same way speech is frequently delayed until the second year and the baby may turn out to be perfectly normal It is particularly suspicious if the baby is backward in several ways

In addition to these negative, as we may term them, phases of development, a characteristic suggestive symptom which appears early in mental deficiency is a tendency toward rhythmic movements Thus a child will sit up perhaps at the proper age, but constantly sway his body back and forth, and I have seen a mentally deficient child otherwise apparently normal in its development constantly change its balance from one foot to the other in a swaying movement when it began to stand This was the first suspicion of the retardation of mental development, at sixteen months in this case Another trait of the mentally backward child is the continuation beyond eighteen months of the use of meaningless sounds which are normal even at twelve months

No definite diagnosis of mental deficiency in a young infant should ever be made upon failure of any one factor in the development, but usually in mental deficiency one sees a general retardation in all of the factors mentioned above In my own experience the most characteristic early sign is the failure of the baby to attempt to hold the bottle when it is being fed Beyond the age of two years a diagnosis of a marked degree of mental deficiency is decidedly easy and obvious One must be most guarded in the diagnosis of deficiency in an infant unless obvious signs of an anatomic or pathologic nature are associated with the backwardness Physical retardation as a result of malnutrition may make a child backward when there is nothing the matter with the brain Moreover, in the case of simple amentia, one cannot tell at an early age just what degree of mental retardation is

present and not infrequently infants who seem quite hopeless progress to a mental age of several years

Leaving now the question of infancy, we come to the group of children in which the physical development, as a rule, has been little if any retarded, but in whom there is a definite backwardness Frequently in these children there is little if any suspicion of mental retardation in infancy and the suspicion is first aroused in early childhood or when the child attends school In the past these children have usually been referred to as "queer" and no real idea of mental deficiency had been present. This is the field of diagnosis and study which was largely opened up through the epoch-making work of Binet, a pioneer in the field of mental and intelligence testing Binet devised a series of graded problems designed to test the native intelligence of children at different age periods rather than intelligence or knowledge acquired through school or home training Binet's first group of tests lie within the age of intelligence of the normal three-year-old child, and the rest are graded up to the age of fifteen, together with an adult list Following Binet's death in 1911 this work has been carried on by numerous psychologists and a number of scales have been supplied by different workers for the measurement of intelligence One of the most useful of these is the so-called Stamford modification worked out by Prof Terman and his coworkers In the last decade these tests have not only been used for the determining of mental retardation, but they have found wide application by psychologists in determining the tendencies of the individual along different lines of activity and in determining unusual mental superiority as well as deficiency Many of the tests which have been devised require special apparatus and all require a rather definite method of asking and giving the questions in the various tests

Those of us who deal with children are particularly interested in the tests of the first three years The original Binet tests for the third, fourth, and fifth years are as shown on page 62

Age three
Points to nose eyes, and mouth
Repeats two digits
Enumerates well-known objects in a picture
Gives family name
Repeats a sentence of six syllables

Age four
Gives his sex
Names knife and penny
Repeats three digits
Compares two lines

Age five
Compares two weights
Completes a square
Repeats a sentence of ten syllables
Counts four pennies
Unites the halves of divided rectangle

Many children of four or five years can do the tests of children a year or more older, but a child of four or five who cannot do the tests for his age is usually decidedly backward An excellent book on the subject is that of Prof Terman on "The Measurement of Human Intelligence"

Management of the Defective—The mentally deficient infant or child presents a problem in management rather than treatment, for in only one type—cretinism—is therapy of any avail in improving the mental condition Our problem is rather one of developing to its fullest extent the mentality which exists in each individual case and in developing a program of life for the individual patient As Dr John Thompson, of Edinboro, so aptly states it, we must always keep in mind that "not only is the child not like other children, but that, except in the rarest cases, *he will never become so*" Our problem is a broad and complicated one and we must take into consideration in each individual case not only the immediate care and training of the baby, but the environmental surroundings, the type, character, and intelligence of

the parents (especially the mother) the position of the child in the family—whether an only child or one in the midst of a family of normal children—and the economic and social status of the parents

Perhaps it is well to discuss first of all the problem of informing parents that their child is mentally backward This is anything but an easy task and each time I am up against the problem I end by being quite sure that the next time it has to be faced my attitude will be quite the reverse You can be quite sure that the vast majority of parents will not only be resentful but will be absolutely positive you are wrong in your diagnosis, and I know some parents who have never been willing to admit that their child differed in any way from a normal child even though their child was a hopeless defective obvious to every one To begin with one should never make a snap or abrupt diagnosis Even though the condition is obvious nothing is to be gained by haste and the physician s problem is as much to help the parents as it is to help the child Our attitude must be guided of course as to whether the infant is seen in our regular practice or the consulting room In the latter case we can be sure the infant has been or will be bartered around from physician to physician and in time to faddist or cultist until some one is found who promises a cure One can hardly blame the parents of a mentally defective child from trying everything from osteopathy to Christian Science and when they finally come back for advice having realized you have been honest, I can never find myself censorious but sympathetic, over their efforts When the parent comes to the consulting room with a mentally defective child I never try to find to whom they have been or what they have been told as one can be certain they are after a different opinion and this almost without exception one cannot give Under these circumstances it is best be frank—not brutal—helpful and hopeful—not despondent but above all to be truthful You know that the first shock is over and that telling the parents the child is backward will not upset their balance

In one s own practice the problem is different. Here except in the case of obvious pathologic conditions the state of affairs

slowly makes itself manifest to the physician through the failure of the child to develop as outlined above Watch the infant and help the mother in her efforts to train the child By the time the parents note the backwardness you have, as a rule, definitely made up your mind that a condition of backwardness actually exists Sooner or later the mother will begin to note that her baby is "slow" in developing and will question you You can be quite sure that the mother has been thinking about it for some time before she questions you Unless there are some extraneous reasons making it necessary for you to make known the condition of affairs before, this in my experience is the time to tell the parents definitely that the child is backward—not mentally deficient or an idiot or an imbecile You can with honestly tell them two things in regard to the backwardness at this time—first that it is impossible to know the degree of retardation that will persist and secondly that the future will depend more upon the mother's care and attitude than upon any other factor Even if the infant seems to be in a bad way, nevertheless it is almost always possible with persistence to widen its activities and capacities Unless every effort is made to train the child, the fullest use of the latent capacities will not be developed and the infant will have a greater degree of retardation apparent than actually exists As a rule, it is never worth while to try and make parents believe a mentally deficient child is *normal* despite the best of intentions, for sooner or later they will hear the truth and a purely humanitarian motive will be regarded as ignorance As a general rule, one can say that, while admitting backwardness exists, the attitude at first should always be that it may be slight and unimportant Prognosis to a parent should be guarded and more hopeful than the case may seem to you as a physician

The most important thing we can do for the mentally deficient baby is to look after its training and nutrition The latter in serious cases is frequently a difficult problem and the poor nutrition is a frequent indirect cause of the death which takes place so often in early life in mental deficiency The condition of nutrition is moreover a determining factor in the training of the

child The chief difficulties one encounters, as a rule, are two one, an inability to get enough food into the baby to make up for the overactivity of a backward child, who so frequently cries more or less continuously and fails to get enough sleep and rest The second problem often seen is to get the baby to take solid or semisolid food after the time has come when supplementary diet must be added to the milk diet the baby has been taking The earlier this is started the better, by the fifth or sixth month at least, as not infrequently it takes several months of daily effort to get semisolid food down and in the meantime the nutritional condition becomes involved while the training is taking place It is not at all unusual to see badly nourished mentally deficient babies of eighteen to twenty months on an almost exclusive diet of milk, and a nutritional state that goes with such a diet If the infant once gets into a bad nutritional state a vicious circle is established, by the deficiency and nutrition reacting upon one another, which is extremely difficult to overcome

The success of training an infant depends almost entirely upon the interest and intelligence of the mother—a point which should constantly be impressed upon her—or in one of those not unusual instances where a nurse develops a maternal instinct for the unfortunate infant and lavishes her attention and love upon her charge

Dr Thompson, who has given so much thought to the subject of the home treatment of defectives, makes the following points in regard to the training of the mother

Encourage the mother to try and make the baby do the things which please her Have her encourage the baby to do over and over again the things the baby likes to do and which bring out its desires and likes Arouse the baby's interest in doing the things he does not attempt because of their difficulty Make every effort to have the baby do things for himself, *e g*, if he likes to hear a rattle persuade him to shake the rattle himself

Habit formation is, of course, difficult and requires infinitely more time and patience than in training a normal baby With persistence and efforts cleanliness can be taught Practically no one but a mother will be interested enough to give the atten-

tion needed to teach control of the bowel and bladder In mentally deficient children they empty at fairly regular intervals as in a normal baby, but the instinct of associating a bowel movement with a chamber is very slow in developing

Speech is usually very slow and requires constant repetition of simple sounds or words associated with movements or objects Walking, too is slow in development and the child needs an unusual amount of effort and training As the child grows older special training in self-control is essential What the physician is called upon to give is constant encouragement and a sympathetic understanding of the difficulties the mother is having

The Mentally Defective and the Family—In infancy the mentally defective child is largely an individual problem his place in the family is more or less the place of any infant except in that he needs more training and attention As he becomes older, however his place in the family group becomes involved and not infrequently a complicated problem develops Where the degree of mentality never passes that of an infant the child is better off, as a rule, in an institution unless the economic situation is such that proper quarters and attendants can be provided for, without injury or harm to the other normal children if such there be In fact, the effect of an abnormal child upon the development of other normal children must always be taken into consideration and every effort be made not to let them be harmed by the presence of a defective Quite unintentionally and without thought of its effect upon the others, parents are apt to give too much attention to the defective to the neglect of the others Instances are not infrequent where parents in a poor economic condition have even gone into debt to lavish care on a defective who cannot be helped much to the detriment of the other children While such an attitude can be understood from a sentimental standpoint it is unfair to the others and thus frequently needs to be made clear It is impossible to get away from economic considerations in considering the management of defective children

Let us consider the child who has a mental age of six or seven or thereabouts While such children are not capable of a school

education much can be done for them and they can be made happy if their life is adjusted to their mental capacity For such children manual labor or occupation such as they can do must be provided and if they are kept busy they are usually happy Many of the so-called "village fools" are in this class and many of them through steady work or odd jobs fitted to their intelligence become self-supporting and are happy The higher grades of mentality—the moron group—usually adjust themselves to their surroundings and life, provided they are put in a position not calling for intelligence above their capacity and ability It is sometimes difficult to make people see that their child is happier living a simple life at regular manual labor than when it is attempted to place him in a position or among people who are on a higher mental plane The essence of the problem is to place the mentally defective in such surrounding as will fit in with the degree of mental ability present, for it is only in this way that we can expect him to be happy

CLINIC OF DR ALEXIS F HARTMANN

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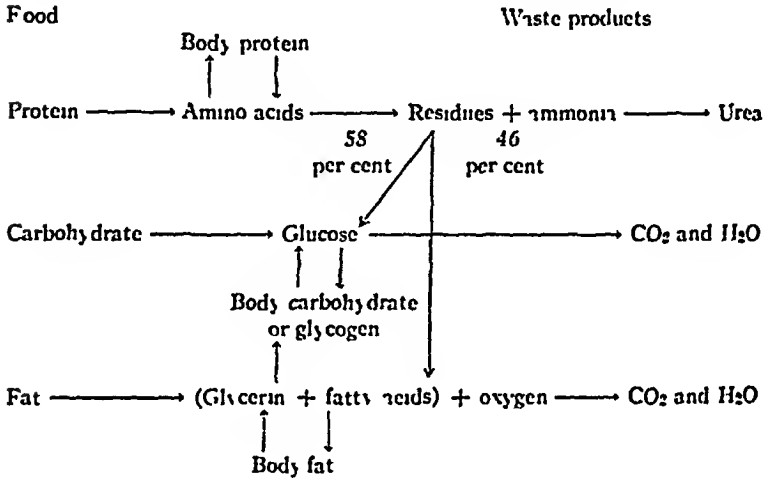
DIABETES MELLITUS IN INFANTS AND CHILDREN

IN infants and children diabetes mellitus is seen usually as an uncomplicated disease, and apparently results from a failure on the part of the pancreas to secrete "insulin" normally When insulin is furnished properly from an external source this failure should not be felt There remain, however, several problems of more or less fundamental importance, chief among which are the nutrition and growth of the patient, the maintenance of his natural or *autogenous* tolerance, and the partial restoration of lost tolerance

Let us consider first the question of nutrition and growth It is to be conceded at the outset that our diabetic patient should grow and develop as a normal child would In general, it may be said that the nutrition and growth depend upon the diet, the insulin effect, and general hygienic care The first task lies in the calculation of a theoretic diet, which is based upon the following considerations (1) Caloric requirement, (2) protein requirement, (3) optimum carbohydrate requirement We have found it quite unnecessary to determine the patient's basal metabolism and then increase the diet to cover the energy requirement of growth and activity Instead, a diet is immediately calculated which covers, or which should cover, these three requirements, and also allow for the energy lost in the excreta The work of Holt and Fales[1] on the energy requirement of normal children furnishes the basis for this approximation In general, the caloric figures for the diabetic are identical with those of

[1] Holt and Fales, Amer Jour Dis Child, vol 24, p 316, 1922

the normal child except when activity is limited for some special reason The next step is to distribute the calories between protein, fat, and carbohydrate in such a manner that there is a safe antiketogenic-ketogenic balance, so that ketosis would not exist if the actual body metabolism approximated at all closely the dietary mixture The following diagram illustrates the interrelation of food-stuffs and actual metabolism



The protein allotment is next fixed because it is very important Enough must be given to permit the building up of new tissue associated with growth, but a great excess is to be avoided because of its conversion into glucose and its "specific dynamic action" in stimulating total metabolism It has been found that in infants and young children quite as much protein must be given to the diabetic as to the normal In the older child less protein can be given The following table is quite helpful in estimating the caloric and protein requirement of children of varying ages, the larger figures being used when the infant or child is much under weight The smaller figure may be used if the patient's ideal weight and not his actual weight is used

Age (in years)	Calories per kilo body weight Normal	Calories per kilo body weight Diabetic	Grams per kilo body weight Normal	Grams per kilo body weight Diabetic
1	100–120	100–200	4 0	4 0–6 0
2	90	90–150	3 5	3 5–5 0
4	80	80–100	2 9	3 0–4 0
6	80	70–90	2 9	2 5–3 0
8	80	60–80	2 9	2 0–2 5
10	80	50–70	2 9	1 5–2 0
12	80	50–70	2 9	1 5–2 0
14	80	50–70	2 9	1 5–2 0

With the total caloric and the protein requirement decided upon the CH and the F allotments are arrived at through the use of Shaffer's[1] formula By way of example a diet is calculated rather simply as follows

If we have a diabetic child six years of age and weighing 44 pounds (20 kg) the caloric requirement is

$$20 \text{ kg} \times 70 \text{ cal} = 1400 \text{ cal}$$
$$P = 20 \times 2 = 40 \text{ gm}$$

Minimum carbohydrate is estimated by the use of Shaffer's formula

$$S\ F = \frac{\text{total metabolism} - 100 \times \text{urine nitrogen}}{50} = \text{grams carbohydrate necessary to prevent ketosis}$$

It is unnecessary actually to determine the urinary nitrogen A figure approximating the true value can be estimated if we assume that 75 per cent. of the dietary nitrogen will appear in the urine Dietary nitrogen would be

Protein × 16 per cent = 40 × 16 per cent or 6 4 gm
Urinary nitrogen will be 75 per cent of 6 4 gm = 4 8 gm

$$\text{Then, } \frac{1400 - 100 \times 4\,8}{50} = \frac{920}{50} = 18\,4 \text{ gm carbohydrate minimum}$$

If this figure were used ketosis would not exist *if* the actual metabolism were as calculated *i e*, 1400 calories and if the fat and carbohydrate were burned uniformly over the twenty-four

[1] Shaffer P A, Jour Biol Chem, vol 54, p 440, 1922

hours Since these assumptions may not always be true, and since a diet yielding 1400 calories and containing only 18 4 grams of carbohydrate would be unpalatable and refused by the small child, we have found it much better to double this minimum figure, making the optimum carbohydrate about 40 grams The fat then is obtained by subtracting the combined protein and carbohydrate calories from the total calories as follows

$$\begin{aligned} \text{P cals} &= 40 \times 4 = 160 \\ \text{CH cals} &= 40 \times 4 = \underline{160} \\ \text{P and CH calories, total} & \quad 320 \end{aligned}$$

$$\text{Fat calories} = \frac{\begin{array}{r} 1400 \text{ calories} \\ -\ \underline{320} \quad " \end{array}}{1080 - 9 = 120 \text{ gm}}$$

Calculated in this way the diets are usually found sufficient for the patient's need for a considerable time The protein is derived chiefly (75 per cent) from milk, eggs, and meat The carbohydrate exists largely in the fruits and vegetables of the 5 to 10 per cent class We have found it usually most convenient to divide this diet into three equal meals

The diet for a young infant will be discussed later

INSULIN REQUIREMENT

The initial adjustment of insulin dosage is accomplished in this manner Before the patient is given the theroretic diet the blood-sugar is brought down to normal by a short fast (omission of one or two meals) plus insulin, the insulin being given either empirically at four-hour intervals, until the desired result is obtained, or given in a single dose calculated to "take care" of all the excess glucose in the body, assuming that body fluids comprise two-thirds of the body weight and are of the same concentration of glucose as the blood, and that 1 unit of insulin will remove 1 5 to 2 gm of glucose By way of example, the dosage for T M when he was readmitted to the hospital on December 31, 1924 was calculated as follows

Wt = 55 lbs (25 kilos)
Body fluid = 25 × $\frac{2}{3}$ = 16 7 kilos
Blood-sugar on admission was 0 500 per cent
Approximate glucose content of body = 16 5 × 005 = 82 5 gm.

Since the blood-sugar is five times the normal value, insulin should be given in sufficient amount to remove four-fifths of 82 5 gm , or 66 gm glucose

If we assume that one unit of insulin will take care of from 1 5 to 2 gm glucose, and use the average 1 75, our dose would be 66 — 1 75 = 38 8 units

Actually 40 units were given, and in four hours the blood-sugar fell from 0 500 to 0 082 per cent , a figure which was quite close to the desired one (0 100 per cent)

This method of calculation usually works well when used such factors as loss of glucose in the urine and formation of glucose from protein metabolism apparently balancing each other It would be safer, however, to consider that 1 unit of insulin would take care of 2 gm of glucose.

When the blood-sugar is normal the diet is begun If the patient shows no sugar and the blood-sugar remains within normal limits, no insulin is necessary If, however, glycosuria accompanies such a diet, insulin is given in amount sufficient to maintain normal blood-sugar and prevent glycosuria This is sometimes done by giving 1 unit for each 1 5 gm of glucose excreted per day, but is usually given in empirical doses based on experience The number of injections depends upon the severity of the diabetes In the very mild diabetic the blood-sugar falls during the night and rises during the day, after meals and with activity If his daily requirements does not exceed 10 units, all can be given in a single injection before breakfast which is made the largest meal Even such a case, however, is more easily controlled by two daily injections, one before the morning and the other before the evening meal If the amount necessary exceeds 20 units, it is best to give three equal meals and three injections, one preceding each meal If the diabetes is very severe and approaches the "total diabetic" state, the effect of the evening injection will be gone long before the next

morning and the blood-sugar may mount well beyond the threshold In that case the patient cannot be kept entirely sugar free on three injections and must be given a fourth at midnight The following chart (Fig 33) illustrates the behavior of the blood-sugar level of cases of varying severity In the less severe cases it is comparatively a simple matter to keep the blood-sugar fairly constant within normal limits, but in the "total diabetic" this is not by any means an easy matter, although it can be done in the older children In infants, however, it

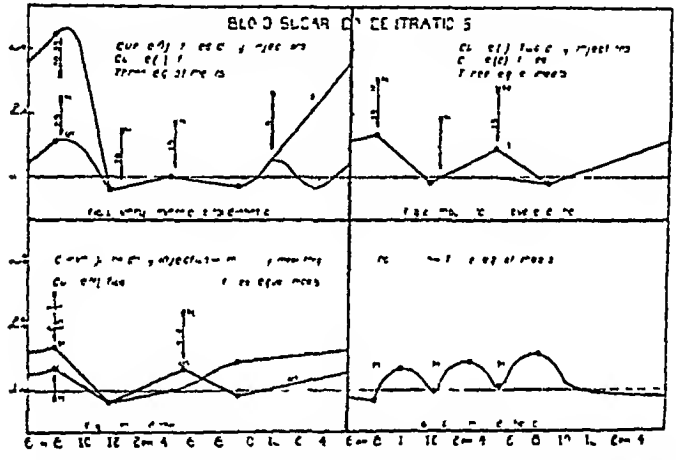


Fig 33 —Blood sugar concentrations of well controlled diabetics (showing the effect of varying numbers of injections of insulin)

becomes a very difficult and sometimes dangerous task, as will be described later

When patients are admitted in coma or with severe acidosis, from experience we know that for a time at least they behave as "total diabetics," and as soon as they are free from ketosis, and have normal blood-sugars, diet and insulin therapy are started on the assumption that they *are* total diabetics *i e*, they are given four daily injections, and receive 1 unit of insulin for each 1 5 gm of available glucose in the diet, until the urine has been free from sugar for two or three weeks, when the insulin dosage

is gradually cut down If a reaction occurs the dosage is reduced sooner

AUTOGENOUS CARBOHYDRATE TOLERANCE

Success in the maintenance and especially in the recovery of the autogenous carbohydrate tolerance depends on several factors, the most important of which are strict adherence to diet and maintenance of normal blood-sugar by adequate insulin dosage If a patient continually shows even small amounts of urine sugar from dietary indiscretions or inadequate insulin dosage the result is inevitable—loss of tolerance and necessity for greater and greater amounts of insulin If however, strict adherence to diet is maintained and insulin is given in sufficient amount to keep the blood-sugar approximately normal, many cases will show at least a temporary gain in tolerance and insulin dosage may be gradually reduced, and in some cases insulin may be temporarily discontinued entirely without return of glycosuria Some cases however, even when kept sugar free for considerable periods of time, show little or no recovery In general the more acute the disease and the shorter the duration before efficient therapy is instituted, the more rapidly and extensively recovery of tolerance takes place On the other hand in the longer standing diabetic and in the infant whose urine cannot be kept sugar free, recovery takes place very slowly, if at all Another very important factor is infection, such as the ordinary cold acute tonsillitis, or alveolar abscess from carious teeth With such an infection a child maintaining or recovering tolerance may very rapidly lose it, and apparently from a cause more specific than just stimulation of metabolism and resulting excess and loss of carbohydrate tolerance

There is another factor important and but little understood, and that is the tendency which is inherent in this disease to lose tolerance and which must be linked closely with the still unknown cause of the disease In as short a time as one year this tendency becomes manifest even in cases which have exhibited early remarkable recovery of tolerance

DIABETIC ACIDOSIS AND COMA

Evidence points strongly to the fact that diabetic acidosis is due almost entirely to the acetone body acids, *i e*, from ketosis Theoretically ketosis exists or should exist when the metabolic ratio $\frac{\text{fatty acid molecules}}{\text{glucose molecules}}$ exceeds 2 to 1 (Shaffer) Practically, ketosis exists when (1) too little insulin is given, (2) when there is not sufficient available carbohydrate in the diet, (3) when metabolism is increased either from undue amount of work or by infection As soon as aceto-acetic acid and beta-oxybutyric acid are formed, they are neutralized by alkali, drawing upon the sodium bicarbonate of the blood-plasma and tissues, as this is the most readily available alkaline buffer Since the acidity of the blood depends upon the ratio $H_2CO_3/NaHCO_3$ the carbonic acid must be eliminated as rapidly as the sodium bicarbonate is reduced by neutralization of these acids This is effectively accomplished by increasing the ventilation of the lungs *Thus* increased ventilation constitutes the hyperpnea, or air hunger, characteristic clinically of acidosis Acetone exists on the breath, can be smelled or tested for by blowing through Scott-Wilson reagent Diacetic acid appears in the urine, and—a matter of importance—the reaction of the urine becomes acid to such an indicator as bromcresol purple If freshly voided urine is alkaline we can be almost certain that acidosis does not exist despite the fact that there may be considerable diacetic acid in the urine [1] If the patient is not treated the acidosis becomes more severe and the alkali reserve is further reduced, the patient becomes comatose, and usually becomes anhydremic from (1) reduced fluid intake, (2) excessive water loss (polyuria), and (3) vomiting Of itself, severe anhydremia is a matter of great concern, and in the comatose diabetic it affects very badly the ultimate prognosis It is well known that in anhydremia urine is excreted in scanty amounts and usually contains much albumin and shows granular and hyaline casts, and that non-protein

[1] The converse, however, is not true The mere presence of acid urine does not necessarily mean acidosis Also the presence of acid urine does not rule out alkalosis (Alkalosis existed in an infant with severe "pyelitis" The urine was persistently acid to bromcresol purple)

nitrogen accumulates in the blood It is possible also at this stage that there is a lessened excretion of acid sodium phosphate and that the kidneys are less well able to manufacture ammonia from urea to replace sodium when excreting the organic acids and salts In marked cases even the acetone bodies themselves are not excreted Finally the acidity may become so great that either the patient dies at once or some irreparable damage takes place in the body cells, and the patient dies even when the plasma bicarbonate has reached a normal figure

Treatment for acidosis should begin with the prevention of ketosis One should be certain that the diet is not essentially ketogenic in nature and that sufficient insulin is given to permit the body to utilize glucose and its antiketogenic nature In many cases, however, acidosis occurs, and when it does it results either because there has not been strict medical supervision of diet and insulin dosage, or because a superimposed infection results in increased metabolism, loss of carbohydrate tolerance, and ketosis The first essential is to increase the carbohydrate metabolism by giving insulin In severe cases the intravenous method is the route of choice In comatose patients with anhydremia the administration of water is of great importance. Since these patients vomit easily, water can best be given as Ringer's solution subcutaneously The advisability of giving alkali (sodium bicarbonate) is debatable Likewise is the administration of glucose Certainly patients recover from diabetic coma with insulin therapy without the administration of sodium bicarbonate, since the sodium ion is liberated when the organic acid radicle is oxidized, and may combine with carbonic acid to replenish the sodium bicarbonate of the blood On the other hand, through excretion of sodium salts of the organic acids a certain amount of sodium must be lost from the body and when the plasma bicarbonate becomes as low as 10 to 15 volumes per cent we rather feel that an initial dose of sodium bicarbonate is beneficial Certainly, too much sodium bicarbonate can produce much harm When the sodium ion is liberated from organic salts the bicarbonate of the blood increases from this autogenous source, and if additional bicarbon-

ate has been given, alkalosis may result and patients may die from this cause It is rather to the point that clinically a patient rapidly recovering from very severe acidosis and coma breathes naturally and easily when the plasma bicarbonate has risen only to 25 to 30 volumes per cent , which can only mean that the CO_2 tension is likewise reduced and the ratio H_2CO_3/-$NaHCO_3$ is at its normal figure, 1 to 20 Through the action of insulin on the oxidation of glucose and organic acids the $NaHCO_3$ is increased much more rapidly than free CO_2 can be accumulated

It has been stated by some observers that the diabetic acidosis can be caused by acids other than of the acetone body type As proof of this assertion these observers have mentioned the fact that occasionally cases have shown little or no diacetic acid in the urine Such an assumption is probably incorrect since in the anhydremic state the kidney fails to excrete such products as acetone body acids as well as non-protein nitrogen This is very well demonstrated by Adeline S (Fig 45), whose urine when she was in coma contained only a trace of diacetic acid at a time when the blood contained a very large amount (78 mg per 100 c c)

The use of glucose in diabetic acidosis is recommended by some, condemned by others Those who use it feel that it lessens the danger of hypoglemic reactions and makes safer the immediate administration of large doses of insulin Joslin, however, is strongly antagonistic to its use, basing his stand chiefly on the fact that there seems to be a maximum rate at which the human organism can oxidize glucose, and giving more of it will not increase this rate, and must only overload the diabetic and be removed at some later time We have used glucose in some of our cases, and in one, Adeline S , we feel that its use was beneficial perhaps for an entirely different reason When a diabetic patient fails to recover, even though the plasma bicarbonate be raised to a normal figure, it is usually found that there is marked impairment of kidney function and that little urine is passed With sufficient water administration intravenous hypertonic glucose is a good diuretic At any rate

following its administration Adeline S began to secrete urine rapidly which was full of albumin and casts after a period of anuria

INFANTS WITH DIABETES

The same general principles concerning treatment of children also apply to infants, but their execution is not always easy In the first place, the diet must be one suited to an infant and yet be a good "diabetic diet" Milk is the basis of the diet of a normal infant under two years of age A quart of milk, however, contains about 40 gm of lactose and is therefore, not desirable from the diabetic standpoint If however the lactose can be removed from the milk the protein and fat remaining could be utilized This can be done by precipitating the casein with some such product as chymogen and straining off the whey which contains most of the lactose The casein and most of the fat remain as curds Specifically, 1 teaspoonful of chymogen is added to 1 quart of milk, and the mixture allowed to stand one-half hour then strained overnight through cheese-cloth The moist curds prepared in this way from 1 quart of milk weigh about 150 gm and contain about 25 gm protein, 25 gm fat, and 5 gm C H They can be fed as such, or shaken with water and fed from a bottle as milk In addition some whole milk can be fed, which ought not to exceed a pint Fresh fruit or fruit juice, green vegetables, crackers, or bread from bran or diabetic flour, butter and eggs and cod-liver oil constitute the rest of the diet

Arthur B who is now three and a half years old, has been on such a diet since he was first seen by us two years ago Specifically his diet is as shown on page 80

The insulin requirement is reached in the same manner as in the older child but must be watched closely, because it is likely to vary considerably, even from day to day The following factors influence the insulin requirement (1) Poor appetite, reducing particularly the carbohydrate intake, (2) vomiting (3) diarrhea, which prevents complete absorption of carbohydrate, probably because of loss from fermentation by intestinal bacteria, (4) variations in metabolism caused particularly by infection or unusual activity By far the most valuable aid in the regulation

	Gm	P	F	C H	Calories	Available C H
Morning meal						
Curds from ½ quart of milk	50	8 3	8 3	1 6	115 3	
Whole lactic acid or sweet milk	150	5 2	5 2	6 0	65 5	
One egg	50	6 6	6 0		50 4	
Orange (peeled and sliced)	75	0 6	0 1	8 9	38 9	
Butter, Cellu wafers	10		8 5		76 5	
Cod liver oil	4		4 0		36 0	
		20 7	32 1	16 5	382 6	31 6
Noon meal						
Curds from ½ quart of milk	50	8 3	8 3	1 6	115 3	
Whole lactic acid or sweet milk	150	5 2	5 2	6 0	65 5	
One egg	50	6 6	6 0		50 4	
Spinach, cauliflower, cabbage, or carrots	100	1 1 2 1	0 5	2 3 8 2	18 1 42 7	
Butter, diabetic bread	10		8 5		76 5	
Cod liver oil	4		4 0		36 0	
		21 2 22 2	32 5	9 9 15 8	361 8 386 4	25 8 to 39 9
Evening meal						
Cod-liver oil	4		4 0		36 0	
Curds from ½ quart of milk	50	8 3	8 3	1 6	115 3	
Whole lactic acid or sweet milk	150	5 2	5 2	6 0	65 5	
One egg	50	6 6	6 0		50 4	
Tomato (fresh or stewed)	100	0 9	0 4	3 3	20 4	
Dessert (diabetic gelatin)		1 0 2 0			4 0 8 0	
		22 0 23 0	23 9	10 9	291 6 295 6	26 0 27 1
Total		63 9 65 9	89 5	37 3 43 2	1035 0 1064 6	83 4 98 6

of the insulin dosage is the examination of each *individual* urine specimen for sugar, particularly when there is glycosuria, this usually means examining from six to twelve specimens during twenty-four hours The mothers can be relied upon, however, to do this, and usually become very expert Occasionally in the presence of infection hospital admission becomes necessary Not infrequently mild reactions occur, which, however, are controlled by administration of orange juice, and which do not cause the mothers much alarm They learn to recognize the very

beginning of these reactions For safety's sake they are equipped with sterile 5 per cent glucose solution for subcutaneous administration As yet the use of this measure has been unnecessary outside of the hospital

The two youngest diabetics in our series—Arthur B and Billie L—are both practically "total diabetics" Neither can be kept sugar free on three daily injections of insulin Midnight injections, when large enough to keep the blood-sugar from reaching the threshold by the next morning very frequently cause reactions, and for that reason have been discontinued It is very unlikely, therefore, that these children will ever regain tolerance to any material extent

GLYCOSURIA IN INFANTS AND CHILDREN NOT OF PANCREATIC ORIGIN

Many infants and children are sent to the hospital with the diagnosis of diabetes mellitus simply because their urine occasionally or persistently reduces a copper sugar-testing solution In order of frequency the following conditions are responsible for this reduction

(1) *Anhydremia*· Glucose may be present in the urine either because the blood-sugar has risen beyond the normal threshold, or because kidney function is impaired and glucose is excreted despite normal or low concentration in the blood

(2) *Concentrated urine.* The reducing substance is usually *not* glucose, but probably creatinin and uric acid

(3) *Renal diabetes* Certain perfectly healthy children constantly excrete glucose in small amounts independently of diet and blood-sugar concentration These are not cases of incipient diabetes mellitus, in fact, their tolerance for glucose is usually greater than normal The usual kidney function tests are normal Insulin is tolerated in fairly large doses, but does not prevent excretion of glucose It certainly should not be used The diet should be that of the normal child

(4) *Pentosuria*· Common during the summer months when children eat particularly apples and cherries The idiopathic type is rare

TABLE SHOWING EFFECT OF PROLONGED INSULIN THERAPY ON THE CARBOHYDRATE TOLERANCE

No	Name	Age	Admission insulin requirement to remain sugar free	Insulin requirement December 1 1924	Result on tolerance	Remarks
1	F I	17 mos	7/1/24 Admitted in coma			7/2/24 died
2	V B	11½ yrs	9/19/22 Admitted in coma In sulin unstandardized Patient apparently a near total diabetic	45 55 units U 10 80 90 gm available glucose	No effect	Three insulin injections daily Usually glycosuria in early morning Very good co-operation Physical condition excellent
3	R W	3 yrs	12/7/23 No insulin for 59 6 gm available glucose	Not known	Not known	No report since discharge from hospital
4	R I	3½ yrs	11/26/22 Ratio $\frac{\text{gm glucose met}}{\text{U units insulin}} = 1\ 1$	30 units U 10 80-90 gm available glucose Ratio $\frac{\text{gm glucose met}}{\text{U units insulin}} = 1\ 5$ to 1 7	No effect	Three insulin injections daily Glycosuria (15–20 gm) from about 2 to 11 A M Very intelligent co-operation Physical condition very good
5	R D	6 yrs	2/17/23 25–30 units U 10 insulin for 82 4 gm available glucose	20 units U 10 insulin for 82 4 gm available glucose	Slight gain	Two insulin injections Usually sugar free Good co-operation Physical condition normal
6	I S	6 yrs	8/3/21 45 units U 10 insulin for 90 gm available glucose	25 units U 10 insulin for 88 gm available glucose 11/11/21	Gain	In hospital entire period Physically normal
7	G W	6½ yrs	4/19/23 No insulin necessary for 110 gm available glucose	Not known	Not known	Lost tolerance shortly after discharge following severe sore throat and nasal infection Lost track of later
8	C L	7 yrs	4/11/23 Admitted in coma			1/12/23 died
9	H R	7 yrs	2/11/24 Admitted in coma			2/15/24 died
10	W R	9 yrs	2/10/24 No insulin necessary for 97 gm available glucose	5 units U 10 insulin for 96 3 gm available glucose	Loss without insulin Recovery with insulin	Developed glycosuria 9/1/21 Admitted to hospital 10/18/24 Required 20 units U 10 for 81 gm available glucose
11	F M	8 yrs	12/23/23 30 units U 10 insulin for 107 7 gm available glucose	No insulin necessary for 107 7 gm available glucose	Gain	Insulin discontinued in April 1924 sugar free without insulin until August 1924 Since then occasionally glycosuria controlled by insulin Frequent colds

12	N G	8½ yrs	6/2/23 10 units II 10 Iletin for 121 gm available glucose	50 units U 10 Iletin for 89 gm available glucose	Loss	Following severe mouth infection (abscessed teeth) lost practically all of tolerance Required four daily injections Lately midnight dose omitted without glycosuria
13	R M	9 yrs	4/2/23 16 units II 10 Iletin for 102 2 gm available glucose	402 units U 10 for 90 gm available glucose	Early gain, followed by loss	Sugar free without insulin from May, 1923 to March, 1921 Insulin necessary since Several respiratory infections
14	C B	9 yrs	6/13/22 No satisfactory estimate of tolerance			Died 7/20/23, immediate cause bronchopneumonia Had cirrhosis of liver, with portal obstruction Fibrosis of pancreas and spleen Wassermann negative
15	F H	9 yrs	12/29/23 45 units U 10 Iletin for 98 8 gm available glucose	15 units U 10 for 98 6 gm available glucose	Early gain, followed by loss	Sugar free with only 8 units U 10 Iletin from 3/1/24 to 8/1/21 Good co-operation
16	M J	9 yrs	11/17/22 20 units II 10 Iletin for 101 gm available glucose	Not known	Not known	Lost track of
17	J N	9 yrs	8/12/23 required no insulin for 116 3 gm available glucose	30 units U 10 for 116 3 gm available glucose	Loss	Numerous dietary indiscretions 4/19/24 required four daily injections to keep blood-sugar normal
18	C P	9 yrs	11/19/23 15 units U 10 for 90 9 gm available glucose		Loss	Died in July, 1921, after discontinuing diet and insulin and taking up "Christian Science"
19	I B	11 yrs	1/9/21 10 units U 10 for 90 4 gm available glucose	30 units U 10 for 90 4 gm available glucose	Slight gain	Good co operation and strict adherence to diet Few mild infections Urine kept sugar free
20	V N	11 yrs	1/6/23 Admitted in coma	60 units U 10 for 90 8 available glucose	Early gain, followed by loss	See graphic charts (Figs 40-42) Very poor adherence to diet and insulin dosage Severe mouth infection (abscessed teeth)
21	W B	11 yrs	1/19/23 No insulin required for 173 7 gm available glucose	Not known	Loss?	Was taking insulin when last heard from
22	M H	12½ yrs	10/29/23 15 units U 10 for 79 3 gm available glucose	No insulin required for 116 3 gm available glucose	Gain	Very good co-operation Adherence to diet See graphic chart (Fig 48)

TABLE SHOWING EFFECT OF PROLONGED INSULIN THERAPY ON THE CARBOHYDRATE TOLERANCE—*Continued*

No	Name	Age	Admission insulin requirement to remain sugar free	Insulin requirement December 1, 1924	Result on tolerance	Remarks
23	C A	13 yrs	4/7/22 No insulin required for 100 gm available glucose	Not known	Not known	Lost track of
24	R D	13 yrs	12/28/23 Tolerance = 120 gm total available glucose	80–90 units U 20 for 112 8 gm available glucose	Loss	Frequent dietary indiscretions Seldom sugar free Several respiratory infections Four insulin injections at present time, with urine usually sugar free
25	A S	13 yrs	10/8/23 Admitted in coma 70 units H 10 for 105 gm available glucose	10–20 units U 10 for 105 gm available glucose	Gain	Intelligent co-operation No severe infection Kept sugar free See graphic charts (Figs 45–47)
26	C R	14 yrs.	11/10/23 No insulin required for 125 gm available glucose	No insulin necessary for 114 gm available glucose	Still maintained	Intelligent co-operation Few dietary indiscretions Few respiratory infections accompanied by transient glycosuria
27	I H	15 yrs	7/8/23 15 units H 10 for 107 4 gm available glucose	Requirement unknown Given inadequately	Loss	8/24/24 40 units U 10 for 81 8 gm glucose Very poor, unintelligent co-operation Frequent dietary indiscretions

(5) *Chronic nephritis* Not uncommonly in chronic interstitial nephritis, associated with general capillary damage, and elevated blood-pressure, glucose is constantly excreted in the urine as in the renal diabetic In our cases glucose was identified by fermentation tests and osazone reactions, and the blood-sugar was found normal or subnormal when determined by a copper reduction method

(6) *Cachexia* When as a result of chronic infection, the body tissues in general seem severely damaged, glucose may appear constantly in the urine, despite normal or subnormal blood-sugars This type probably also represents kidney leakage

(7) *Alimentary glycosuria*

(8) *Brain injury* Very infrequent

Diabetes mellitus can be ruled out with certainty if there is a normal sugar tolerance, as determined by the administration of 1 75 gm glucose per kilo of body weight (*ideal* weight in fat individuals) in 200 c c water on a fasting stomach, and observation of the effect on the blood-sugar concentration Even the mildest diabetic shows a much decreased tolerance

PROTOCOLS OF REPRESENTATIVE CASES

Case 1 —Arthur B (Infantile type No recovery of tolerance)

This patient has been treated since September, 1922 Diabetic symptoms first appeared at the age of one year, and slowly progressed until the infant was eighteen months of age, when he was brought to the hospital for treatment in an athreptic, semicomatose state, with severe acidosis After nine days of alkali and restricted diet treatment there was still considerable ketosis and glycosuria Insulin made by Professor P A Shaffer, in the Biochemical Laboratory of the Washington University School of Medicine, was then obtained, and with its use the patient was kept alive for four months During this time he had repeated infections, including paronychiæ, rhinitis, tonsillitis, otitis media, bronchitis, and bronchopneumonia When the supply of insulin ran short, acidosis, often severe, would quickly ensue During the last eighteen months he has been treated with

Lilly's dietin, with strict adherence to the diet Every effort was made to keep him sugar free for the entire twenty-four hours of the day with insulin given before each of his three meals, the dosage of which was regulated by examination of *every single* specimen of urine, and by numerous blood-sugar estimations At the very beginning of the treatment this end could be attained, and for a short time his carbohydrate tolerance seemed to increase materially It is noteworthy, however, that at this time he was having a gastro-intestinal disorder with diarrhea, and the increased tolerance was perhaps more apparent than real because of a failure to absorb ingested carbohydrate on account of excessive bacterial fermentation and rapid intestinal peristalsis It was not long, however, before insulin given thrice daily failed to prevent hyperglycemia and glycosuria at night, sugar usually being excreted during the period from 2 to 8 A M An attempt was made to give insulin at midnight to prevent this glycosuria, but was soon discontinued because a dose adequate for this purpose almost invariably caused a hypoglycemic reaction For a year and a half this patient has had insulin thrice daily, and has never for any length of time showed sugar in his urine except during the early morning hours His nutrition and state of development have long since reached normal figures his carbohydrate tolerance however, has *not* improved

Case 4.—Billy L (*Infantile type No recovery of tolerance*) This patient has been treated since November, 1922 Diabetic symptoms first appeared at the age of two years His weight was then 29 pounds Symptoms slowly progressed despite restricted diet until the child was three years and nine months of age when he was brought to the hospital in an extremely emaciated condition, his weight with considerable nutritional edema, being only 16 pounds After showing the usual remarkable and speedy improvement that these cases show with insulin he was discharged from the hospital with the proper diet and insulin dosage worked out for him He was brought back to the hospital after a period of three months and again observed His nutrition had improved really too rapidly,

Fig 34—Case 1 Billy L November 26, 1922

Fig 35—Case 1 Billy L November 26, 1922

Fig 36—Case 1 Billy L January 19, 1923

Fig 37 —Case I Billy L April 26, 1923.

Fig 38 —Case 4 Billy L October 20, 1923

Fig 39 —Case V Billy L October 15, 1921

and he had become obese, but this carbohydrate tolerance was still practically zero For the next six months he was not under our care, and while strict adherence to diet was maintained, insulin was not given in sufficient dosage to prevent glycosuria, the average twenty-four-hour output containing approximately from 30 to 50 gm of glucose At this time he was again brought back to the hospital and a very earnest attempt was made to keep him sugar free for the entire twenty-four hours of the day on three daily injections of insulin The result was exactly the same as in the case of Arthur B , *i e* , glycosuria was usually absent during the day, but persisted during the period from 2 to 8 A M A midnight dose of insulin adequate to prevent this glycosuria in his case, even more uniformly than in A B , was followed by a reaction, and was discontinued At the present time his nutrition is very good, his muscular development is not yet normal, but improving steadily, while his carbohydrate tolerance is still close to zero

Case 20 —Vincent N (Figs 40–42) (Rapidly progressive type Coma Recovery of tolerance)

This patient, age eleven years, was brought to the hospital in coma on April 26, 1923 He was without noticeable diabetic symptoms until two weeks before admission, when he suddenly developed polyuria and excessive thirst and a feeling of languor His true condition was not diagnosed by his doctor at that time, and the symptoms very rapidly progressed, and after only two weeks he was brought to the hospital stuporous, with severe acidosis With large doses of insulin he recovered from his acidosis in a most striking manner, and was sugar free at the end of fourteen hours A diet was worked out for him and insulin was given in an amount sufficient to keep him sugar free At first the amount was large, but soon could be gradually reduced without the reappearance of sugar, until finally, only three weeks after admission, he remained sugar free on the same diet without the use of insulin This remarkable recovery of tolerance was maintained for nine months, during which time he reported for observation at fairly regular and frequent intervals Fairly

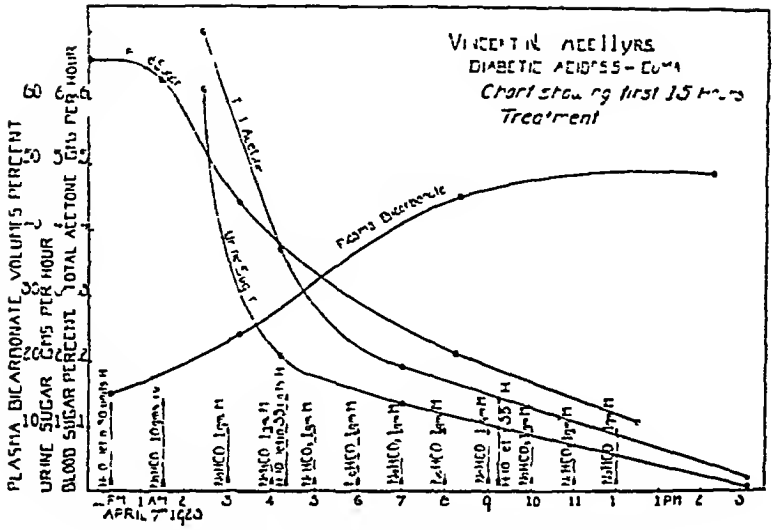


Fig 40 —Showing recovery from diabetic acidosis and coma

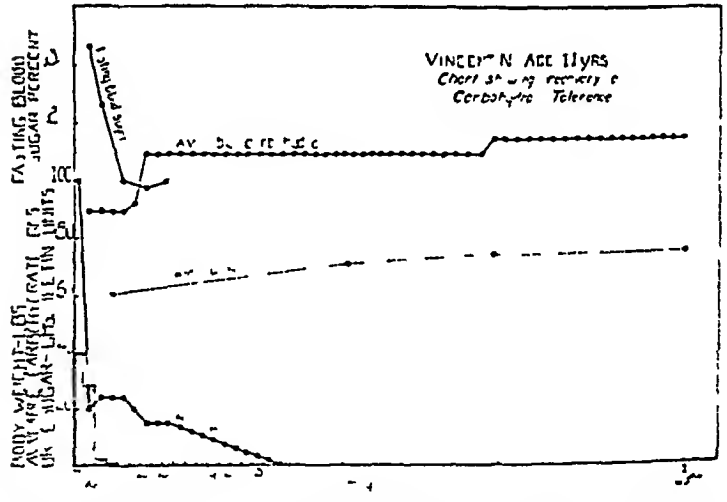


Fig 41 —Showing recovery of autogenous tolerance after urine was kept sugar free

strict adherence to the diet was maintained, I believe, except on two occasions, when he ate candy These indiscretions were

immediately followed by glycosuria, which was checked efficiently by a single dose of insulin At the end of nine months he reported at less frequent intervals and apparently broke diet more often For a whole month he was permitted to have sugar before he was brought back again for observation At this time his tolerance was found to have dropped again to a low level After an unsuccessful attempt to keep him sugar free with administration of insulin and diet while at home, he was again admitted to the hospital Study revealed a low tolerance and difficulty was encountered in keeping him sugar free for the entire twenty-four

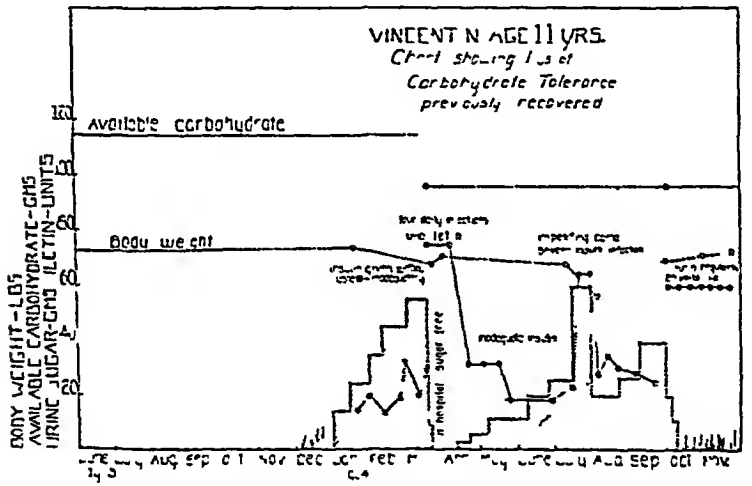


Fig 42 —Showing loss of previously recovered tolerance

hours of the day Toward this end four injections of insulin were given, one before each meal and one at midnight Even with this regulation glycosuria was not always prevented during the early morning hours Throughout most of the year of 1924 insulin was given in quite inadequate doses to prevent glycosuria, and in August, coincident with the development of several alveolar abscesses, he again developed severe acidosis Alarmed again, his parents brought him to the hospital, where it was found that he had lost much weight and practically all of his autogeneous tolerance, and that his insulin requirement was 60

units of U-10 for 90 gm total available glucose At the present time he is getting three injections of 20 units each before meals and usually has slight glycosuria in the early morning hours (Fig 42)

Case 25 —Adeline S (Figs 43-47) (Rapidly progressive type Coma Recovery of tolerance)

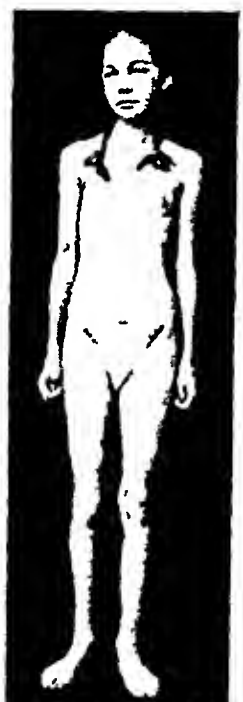


Fig 43 —Adeline S October 24, 1923

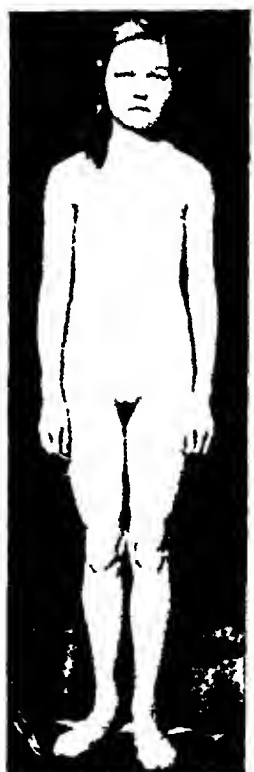


Fig 44 —Adeline S January 9, 1924

This patient, aged thirteen years, was admitted to the hospital on October 8, 1923, in coma She had been well and without diabetic symptoms until about September 5, 1923, when she developed polyuria, unusual thirst and appetite, and began

to lose weight Two days before admission she was compelled to go to bed because of weakness On the day of admission she

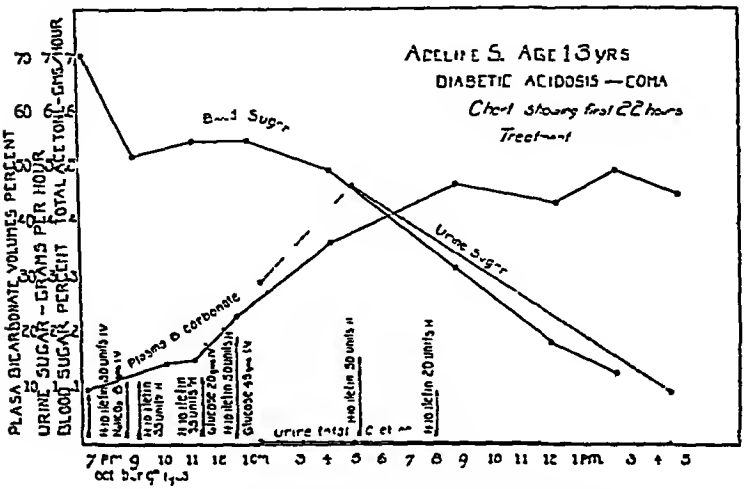


Fig 45 —Showing recovery from diabetic acidosis and coma

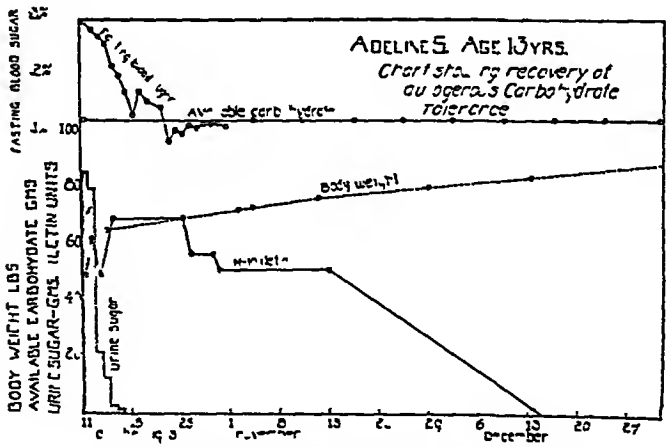


Fig 46 —Showing recovery of autogenous tolerance

became drowsy, and on her way to the hospital, about two hours before she arrived, she lapsed into deep coma She recovered

in a striking manner from her severe acidosis and coma When her diet was worked out and her insulin requirement reached, she seemed to have little or no carbohydrate tolerance To keep her sugar free four daily injections of insulin were necessary, one before each of her three meals and the fourth late at night When discharged from the hospital three weeks after admission she required but three daily injections of insulin, one before each meal The dosage of each of these was daily reduced and the injection before the noon meal was eliminated without the return

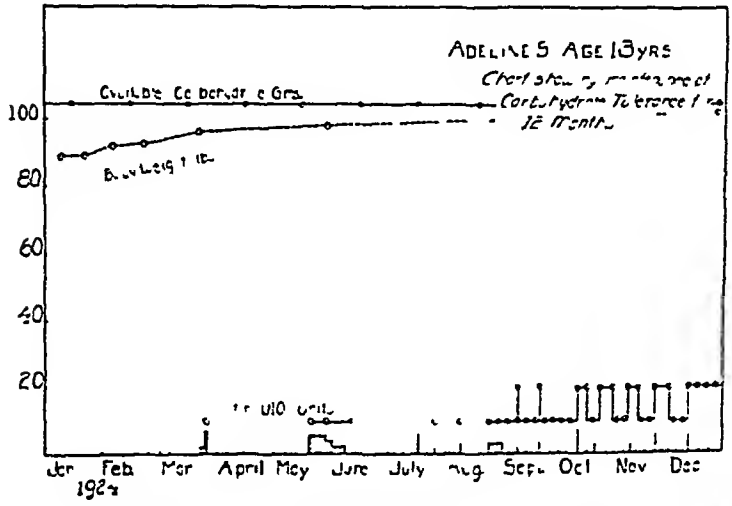


Fig 47 —Showing maintenance of autogenous tolerance and gradual loss at end of first year

of glycosuria Eventually, after a period of about two months, during which time her tolerance was never exceeded, insulin was dispensed with entirely For two months glycosuria did not reappear Then, associated with a bad cold, a short period of glycosuria existed which was controlled with insulin She gained 23 pounds in two months after beginning of treatment, reaching at this time a figure which was normal for her height and age During the eleven months following her admission to the hospital she remained sugar free, gaining weight normally, without insulin During September, 1924 there were frequent

transient attacks of glycosuria, some associated with mild upper respiratory infections, others not attributable to any known cause It was decided to give her regularly 10 units of insulin daily For a month or so this dosage was sufficient to prevent glycosuria, although occasionally 20 units were required At the present time (January, 1925) 20 to 30 units are necessary for a diet furnishing 115 grams available glucose

Case 22 —Martin H (Fig 48) (Rapidly progressive type Recovery of tolerance)

This patient, aged twelve years, was admitted to the hospital on October 29, 1923 Diabetic symptoms were noticeable about

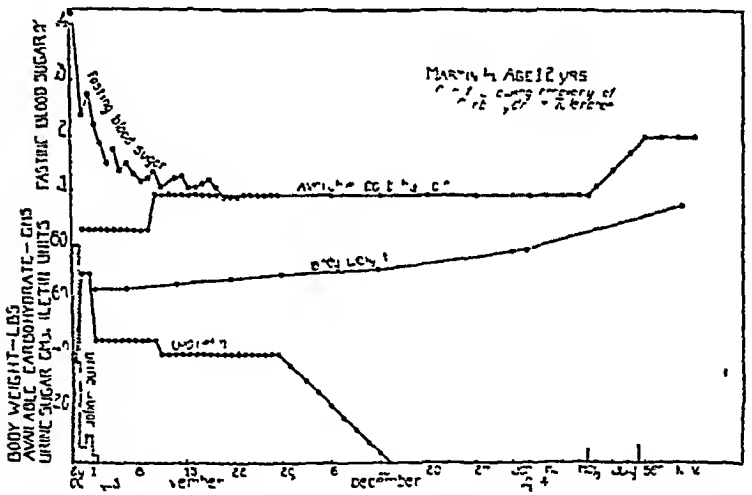


Fig 48 —Showing recovery and maintenance of autogenous tolerance for eleven months

a month previous to admission Symptoms progressed steadily and rapidly, and when the boy was admitted to the hospital he was moderately emaciated and with severe acidosis, in a drowsy, precoma state After the usual treatment directed against the acidosis, and after the plasma bicarbonate content had increased from 18 to 40 volumes per cent a diet was worked out for him and insulin given in amount sufficient to keep him sugar free

For the first ten days three daily injections were necessary, and at first the fasting blood-sugars in the morning were distinctly elevated When they reached normal insulin could be administered twice daily At this stage the boy was discharged from the hospital, with instructions to adhere rigidly to the diet and insulin dosage and test daily twenty-four-hour specimens for urine sugar He reported at intervals of two weeks for a while He remained entirely sugar free and gained weight, and after two months insulin was discontinued The recovery of tolerance has persisted up to the present time, although during the month of December, 1924 there were several transient attacks of glycosuria controlled by several doses of insulin

Case 24 —Ruth D (Persistent glycosuria and loss of tolerance despite insulin)

This patient, a girl of thirteen years, was first seen by us on December 28, 1922 Her family history is of much interest because her father has had diabetes for at least five years, and an older sister died in diabetic coma in 1920 at the age of fifteen years, two years after the onset of the disease A paternal grand uncle had diabetes also Glycosuria in the patient herself was noted by accident when she was eight years old There were no symptoms at this time A dietary régime was started and the patient did very well Subsequently her periods of glycosuria were the result of gross dietary indiscretions, and occasionally during these periods there were traces of diacetic acid present in the urine During the year before admission to the hospital she grew 2 inches in height, gained 12 pounds in weight, and exercised as a normal child would During her first stay in the hospital (from December 28, 1922 to January 15, 1923) the following points were determined Her height and weight were approximately normal for her age Her muscular development was very good At the time of her admission her blood-sugar was 0 089 per cent and the urine was free from sugar Starting with a diet of P-50, F-100, CH-20, her intake was gradually increased until glycosuria appeared This was during the second day on a diet of P-80, F-140, CH-60, which yielded 1820

calories and 120 5 gm of available carbohydrate Since her weight was stationary and her protein metabolism such that she was just in N equilibrium, it can be assumed that her tolerance at that time was approximately 120 gm of carbohydrate The sugar disappeared rapidly from the urine on a "double green day" She was again given the diet P-80, F-140, CH-60, and again on the second day glycosuria reappeared, very shortly after the blood-sugar had mounted to 0 183 per cent (a normal threshold) It was thought desirable to rearrange the diet, raising the P somewhat and the F to a greater extent, and reducing the CH, but still giving in the neighborhood of 2000 calories. This was done and the patient discharged from the hospital, sugar free, without insulin Almost immediately, however, she showed sugar in the urine, which could not always be explained by dietary indiscretions The available carbohydrate in a diet furnishing 2000 calories could not be reduced much more without necessitating ketosis The total caloric intake could not be reduced and the patient be expected to develop normally Insulin was therefore started under the direction of the girl's regular physician Improvement of the glycosuria was noticed immediately and the girl began to gain weight During the next year the girl developed normally, but it was noted that she required more and more insulin on the same diet to prevent large amounts of sugar being excreted in the urine Glucose in some amount was almost always present in the urine During the fall of 1923, while under Dr Woodyatt's care, it was found that on a diet of P-56, F-93, CH-71, 50 units of insulin were required to keep her sugar free By January, 1924, on the same diet, the patient still put out sugar when getting 92 units of insulin daily During February and March, 1924 her diet was P-60, F-115, CH-80, and she received 35 units of insulin three times a day, and still put out some sugar This glycosuria increased and some days the patient was given 200 units of insulin daily For some two weeks before her second admission to the St Louis Children's Hospital she was receiving 40 units before breakfast and 40 before the evening meal, still puting out sugar, and sometimes having hypoglycemic reactions Her diet

was P-55 F-180, CH-60 Three days before admission, because of the insulin reactions, it was thought safer to cut the insulin to one-half that amount, the 40 units being given before breakfast She developed nausea and vomiting, became dehydrated, and was brought to the hospital, with very severe acidosis, in precoma Her acidosis was treated successfully, and on a diet of P-60 F-180, CH-60 it was found that from 80 to 90 units of insulin were required daily to keep her almost sugar free As in the severe diabetics reported above, in order to keep her sugar free insulin had to be given before each meal and again at midnight, and at the time of discharge from the hospital (April 13, 1924) just two weeks after admission, she still usually showed sugar during the period from 6 to 10 A M Since discharge insulin was pushed to the limit to keep her entirely sugar free, with the hope of improving her tolerance That this hope might be realized to some degree, even at this late stage, is indicated by the fact that she now remains entirely sugar free for several days on the same diet and insulin dosage

SUMMARY

The main problems connected with the handling of infants and children with diabetes mellitus are outlined and discussed The effect of prolonged insulin therapy on the natural carbohydrate tolerance of 27 cases is presented in tabulated form Protocols with photographs and charts of representative cases are indicated

CLINIC OF DR HUGH McCULLOCH

WASHINGTON UNIVERSITY SCHOOL OF MEDICINE AND THE ST LOUIS CHILDREN'S HOSPITAL

POSTURAL DEFECTS AND BODY TYPES IN CHILDREN

THIS child is brought before you today as an example of a condition which is commonly seen among school children or in out-patient or private work Their symptoms rarely are severe enough to warrant hospital admission The child is an example of one of the real problems facing this country today, in that the physical condition and health of the individual concerns the general welfare of the nation She presents many but not all of the features resulting from postural defects associated with her body type

She is eleven years old the oldest of 2 children, whose parents are in well-to-do circumstances The father has good health, but is inclined to be thin and is above average height This family is of Anglo-Saxon descent and are typical average American-born citizens

The child has been more or less normal since birth She was under the care of a physician during her infancy, during which time she grew properly, was in good nutrition and was not ill During her preschool period and since going to school to the present time there has been no major illness which could be related to her present condition She had measles soon after starting to school and has occasional colds, which vary in intensity For the most part the colds are not severe, a "runny" nose for a few days without fever but once or twice a year she is ill, fever of 101° to 102° F for several days, headache in the beginning, lassitude discomfort and soreness in her nose, and sore throat During her convalescence a cough develops which

is non-productive, occurs chiefly at night or after exercise There is no history of bronchitis or pneumonia Her tonsils were removed one year ago on the advice of her physician, hoping to avoid these "colds" She is active, attends school, does well—in fact, is a better than average student, plays hard, has a keen interest in her associates and her daily routine Her diet is proper, but she has always been a small eater, particularly at breakfast She goes to bed at 8 o'clock and is a good sleeper

Her present disturbance began indefinitely some two years ago The major features have been constant and may be told briefly She complains of being tired, particularly during the past two winters at school She complains of this occasionally on arising in the morning, but noticeably in the late afternoon At times she complains of discomfort in her back and legs, this occasionally being actual pain which is experienced on going to bed at night She does not go to sleep promptly, and is inclined to be restless during the first half of the night Her interest in her school work has not slackened, indeed, it seems more and more a responsibility to be fully met She is disinclined to play after school, would rather read She is not emotional, but is not in her previous good spirits Her appetite is now capricious, is small, varies in degree, and she is more inclined to express likes and dislikes, particularly dislikes She says milk makes her "sick" She is inclined to be constipated, has a daily bowel movement, but it is hard and large, and her mother must see that ample fruit and vegetables are provided in her diet She at times experiences some abdominal pain which is poorly localized, not severe, and unrelated to eating or to defecation

She occasionally has headaches in the morning She does not require glasses She gains weight very slowly, though she seems as large as other children her age During the past two summers she has done very well, especially last summer, when she spent a month at the sea-shore During that month and the succeeding month of September she seemed perfectly well, but this winter her symptoms have reappeared She is not ill, but she is also not happy, and her parents are anxious to correct these tendencies

On examination the following positive findings may be noted Her actual body height is 56 inches, her weight at present is 72 pounds According to Baldwin and Wood s Height-Weight-Age tables, she is taller than the average eleven-year-old girl, and her weight should be about 80 pounds Her color is good and she has no anemia She is thin, this being apparent when one observes, in the erect position, her torso and her extremities You will notice that the clavicles are prominent the scapula stands out Her ribs and spinous processes may be seen The chest is well rounded, but the shape is longer and narrower than usual The costal angle is approximately 75 degrees, the ribs are inclined downward at a greater angle, the abdomen is full, particularly in the lower part, the flanks are concave, and the pelvic bones are prominent, with a broad pelvic brim She breathes quietly, chiefly abdominal, though there is a fair amount of chest expansion Her extremities seem long and are noticeably thin, her fingers are tapering Now, on turning her for a profile view, you will see that her head is placed forward, and in order that she may maintain horizontal vision she holds her chin up Her shoulders are pulled forward and it is easy to see her exaggeration of the usual spine curves The dorsal region looks almost "hump backed," with a sternum which is almost straight and is vertical The lumbar spine is also curved more than usual Notice the bulging lower abdomen and the marked inclination of the pelvic crest Also notice how uneasily she stands on her feet, how the tendons at the ankles and feet are continuously moving My interpretation of this movement is that she is constantly making some effort to keep her balance You can readily observe that the axis of her weight is not properly distributed through her spine and legs, so the body is not in an easy, restful position

The examination does not reveal any serious physical defects Her teeth are clean, the one carious primary molar is well filled, the new teeth are erupting in good condition, though they are somewhat crowded, and the central incisors are rotated Her palatal arch is narrow and somewhat high, resembling somewhat a French-Gothic type Her tonsil sites are clean and the exam-

mation of her nasopharynx shows only here and there a few isolated moderately enlarged lymph-tissue nodules Her cervical glands are palpable, but are not hard An x-ray of her chest, which you can see on the screen, shows here and there an increased marking radiating out from the hilus region on either side This marking is probably more increased in the right lower lobe The hilus shadows seem a bit denser than usual The lung field is large and clear The heart is normal in size, shape and position though it seems more vertical than usual The diaphragm is curved and the costodiaphragmatic angle is clear A gastro-intestinal study by fluoroscope and plates revealed no pathologic disturbances of function The stomach was found to be long with the fundus below the level of the umbilicus, the large intestine is redundant, not markedly haustrated, and the region of the sigmoid and rectum seems increased in size and in length At times a trace of albumin has been found in her urine

Briefly, then, she complains of fatigue, headaches lack of appetite, underweight, and occasional colds Her examination has revealed no major defect except her poor posture and her body markings

I consider the basic disturbance in this child to be a body type which is commonly called thin or slender Individuals of this type constantly show all the features she shows in a more or less exaggerated form the long narrow head, high palatal arch, tendency to malposition of the permanent teeth, long slender neck a chest which is long and narrow a straight sternum, ribs pitched high, and a narrow costal angle, a large roomy lung field with diminished lung expansion a heart which is placed vertical, the so-called "hanging heart" but not enlarged, the abdominal viscera are placed low by long and often relaxed attachments with a patulous roomy intestinal tract, the extremities are long, the joints are prone to hyperextension, the muscle groups are small, slender, but have a fair tone

It seems impossible to say in this child what has been the determining factor in producing this picture Her Anglo-Saxon lineage predisposes to this type as it is the predominating type of the pure Anglo-Saxon race Also her father inclines to this

same type so that individual inheritance of type characteristics must be borne in mind I do not see any feature about the child which would make me think she has a disturbance of her internal gland secretions This factor undoubtedly plays some part at times in producing well-defined types of body form How much the balance must be disturbed to swing the form to one extreme or another I think no one is prepared to say at the present time She has not suffered from any constitutional disturbance which would affect her body form as, for example rickets congenital syphilis, etc

As a result of the basic disturbance she has developed postural defects which in general are related to fatigue Her body form predisposes to low muscle tone to hyperextension of all joints and a subsequent increased muscle control to maintain balance to relaxation of ligaments and tendons and to the signs of fatigue Her symptoms and physical signs all can be explained on this base of fatigue Fortunately she is not an advanced case and has missed many other phenomena associated with the condition

Briefly, let me discuss the various manifestations of the fatigue complex associated with her body form She is not a nervous child These children often are The continuous involuntary strain of controlling the body position insufficient rest, undernutrition and a conscious or subconscious realization of inability to "carry on" the daily routine expresses itself by irritability, lack of emotional control mental maladjustments and such traits which are commonly seen in "nervous" children

Failure to gain in body weight is a common story These children are uniformly below weight for their height and I feel that it is impossible to force their weight to where it should be if the body form was average or of the opposite stocky type Many children, like this child, are needlessly restricted in exercise or stuffed with food beyond their utilization capacity with an idea of bringing their weight to a point which is unattainable How much weight such a child may require often is impossible to determine by height-weight-age tables, and one may be forced to utilize other signs of body nutrition Such children

as this girl uniformly show a very rapid growth in body length and this growth may start considerably earlier than the stocky type This girl may easily grow 3 inches even 4, in the next twelve-month period I look on the gain in weight to be one of the most valuable signs in handling these children, and I am convinced that one who is gaining uniformly the proper amount, irrespective of the total weight, will not show signs of fatigue I would consider this child should gain approximately 1 pound a month

A constant expression of the fatigue state which is present is the inability to finish the day's routine without breaking By evening the child is tired, worn out, does not eat a proper evening meal, goes to bed tired, and sleep is delayed and restless After a sufficient rest the sleep becomes profound and quiet, and at rising time this child does not wish to be disturbed "They have slept so hard they have a headache" is the morning story

Many of these children complain of discomfort or pain in their back or extremities This pain may simulate subacute rheumatism, it may be differentiated from such a condition by the lack of objective signs in the joints and the lack of localization The abdominal pain which this girl has may be a result of her constipation, or it may be a sign of the general abdominal visceroptosis

This latter condition often leads to a most interesting and important group of signs, none of which this girl shows There are often gastro-intestinal attacks of one form or another Constipation of the atonic type prevails, large, bulky, hard stools, which at times become light colored when a large amount of soap is present, nausea or vomiting occurs, and smaller children gag or vomit easily Often the child may be "bilious" or have "acute indigestion" Another form occasionally seen is the so-called cyclic vomiting The relation of this phenomena to poor body mechanics and visceroptosis has been well described by Brown and Talbot

Orthostatic albuminuria is another condition commonly observed in these children The albumin which has been found in the urine of this girl is of this origin It is found in the urine

after excessive exercise, at the end of the day, or, more infrequently, it may be present, even 3 or 4 grams, per liter, whenever the body is put in the erect position, or the lumbar lordosis increased Rarely the albumin may be due to a nephritis

Infections of the upper respiratory tract are common The high palatal arch with the resultant crowding of the nasal space predisposes to improper passage of air currents and to disposal of secretion and foreign material from inspired air Infections are prone to occur and recur Many of these children have or develop a generalized infection in the nasal tissue and paranasal sinus spaces In the presence of malnutrition and fatigue this predisposition is further increased

The frequency with which children and young adults are suspected of having pulmonary tuberculosis leads me to sound a warning against making such a diagnosis too hastily in individuals of this sort The repeated upper respiratory infection, the cough, malnutrition, the indefinite but suspicious a-ray of the chest, and deficient chest expansion all suggest such an infection I would advise you to wait for further signs of a tuberculous infection before you too hastily class your patient as such In this connection the treatment directed toward correcting the fatigue and other symptoms would probably be useful for a tuberculous patient as well, and as time passes for observation and further examination the true condition can be realized Such children and young adults may be considered to be predisposed to tuberculosis, and the field would be ripe for the growth of the infection after its implantation

In the time remaining at my disposal I would direct your attention toward a most hopeful side of this problem, that is, its prevention and control I consider this a field in which real constructive work can be done by us all To be forewarned is to be forearmed, and much can be accomplished in preventing poor body mechanics and the resultant inefficiency by observing in the early part of life just what type each individual child resembles When one observes in the preschool period, or more conveniently probably in the early school period, such a girl or boy as this child, to so direct his activities, rest, school routine, posture,

growth and nutrition much can be done to successfully avoid these ailments And this can be done in whole or in part by school or private or clinic physicians Therein lies the greatest hope of all—prevention

In the control and treatment of such conditions as this girl shows I would place most emphasis on three major points (1) posture training, (2) activity, (3) rest It is essential that such children have at least the rudiments of correct body position before any advance can be made The instructor may be either school teacher, nurse, nutrition worker or physician Correct posture should be first-hand information for these groups to impart to children

Given a proper body position, there must be such a balance struck between activity and rest that fatigue disappears from the child's mind The activities of the child must involve both ordinary play and such procedures as might be classed as work As a general rule it seems most desirable to keep the child as active as possible without strain, loss of weight, or signs of fatigue, so that the amount of activity allowed a given child will vary with the child and from day to day A second group of activities involve special exercises directed toward the correction of a defect of a certain muscle group or part of the body These special exercises often are of great value in the more advanced fatigue types Occasionally children may need special instruction in posture training

The third important point is a control of rest, as regards amount, kind time, and character of rest for the individual child A general rule is to provide sufficient rest to enable the child to gain a proper amount of weight and to indulge in the greatest amount of exercise which can be done and at the same time gain weight Most of these children need, or require, a midday rest and they all need it when they first come under our care This midday rest is most conveniently obtained following the midday meal In certain children extremely nervous and undernourished it may be advisable to furnish a short period of rest before this meal with a longer period afterward Sleep during this rest is advisable, but not necessary Relaxation is

necessary This rest will enable the child to carry through to night with less fatigue The rest at night should be long, undisturbed, and quiet It is often useful to give the child a hot relaxing bath after the evening meal and before going to bed All overstimulation in the last two hours before going to bed should be avoided The sleeping room should be quiet simple, clean, and accessible to outside air Light covering, light clothing, and no pillows are necessary It may be of advantage to use a small pillow placed under the shoulders, not the head, especially during the day rest The mattress should be firm and straight and the child should lie on the back as much as possible

Two secondary points of importance are diet and, occasionally, binders or braces The diet must be directed toward the correction of two conditions—the undernutrition and the constipation The diet must certainly contain those food elements which promote proper growth and nutrition The amount of milk will vary with the child's ability to take it without discomfort or constipation The aversion of children to milk is an old story, and is based on preconceived ideas of the parents, lack of proper dietary training, and erroneous statements that milk "disagrees" It is true that some children may not be ble to digest properly and care for a large amount of butter fat, and these children will require a lesser amount Nevertheless, we find many of these children who under proper circumstances will consume 2 or more quarts of milk daily This food merits first place in the dietary The second food group consists of butter fat and eggs, the caloric value of these foods is high they contain large amounts of fat-soluble vitamins, and the egg yolk contains fats and certain mineral constituents like iron sulphur, etc The amount of butter taken will depend on the character of the stools In those cases who have spells of cyclic vomiting it may be necessary to eliminate entirely the fats preceding an expected attack Such children often give warning of an impending attack by the appearance of large light or white colored stools full of unabsorbed soap This child today could safely be given 2 ounces of butter fat and one egg yolk daily

A third food group is the vegetables They are necessary

as available sources of mineral salts, residue, chlorophyl pigment, and vitamins of all three or more kinds Modern cookery has added much to our knowledge of choosing, preparing, and serving vegetables, one of the most important points being the harmful effect of overcooking A fourth group of foods are the whole grain cereals and breads They too contain essential ingredients for proper growth and nutrition Such children should have all white flour breads and milled grain cereals excluded from their diet Fruits of various kinds will be necessary for the correction of constipation Meats and desserts should be used sparingly or not at all until the appetite has improved Proper food habits are quite necessary to bring the child to normal, and many of these children need much training in this

Abdominal binders will be found extremely useful for the improvement of visceroptosis Such binders have been devised by Brown & Talbot Braces may be used to force a correct carriage of the body in extreme cases Abdominal massage is of great benefit to those who have constipation and will assist materially in improving the tone of the anterior abdominal muscles

These children will do well under systematic training and control This control will require endless patience and minute attention to detail on the part of physician and parents It is important to have the child's confidence and enlist his or her aid in carrying out the program Health education in the schools may often turn the tables in favor of such children Occasionally symptoms which have been fixed for a long time will quickly disappear More often the changes come gradually and much time elapses until results become apparent This child has reached a very important period, for the physiologic changes and strains of puberty occurring the next few years will need to be met If we can put her in good position with a good nutrition now, she should emerge from puberty a fully developed and physically efficient individual

CLINIC OF DR WILLIAM W GRAVES

ST LOUIS UNIVERSITY SCHOOL OF MEDICINE

SOME OF THE FACTORS UNDERLYING ACCURACY IN CLINICAL DIAGNOSIS

ACCURACY in clinical diagnosis implies the positive recognition and differentiation of morbid processes in the living Because it is the foundation of treatment and prognosis accurate diagnosis should be the goal of every physician It is often an easy task to say the individual is sick, but it is seldom easy to say precisely what ails him To determine precisely what ails the sick is to make accurate diagnoses These are possible in some and doubtful in some, but in most cases our diagnoses are partial, probable, or highly probable

An accurate diagnosis is more nearly possible today than ever before, because medical knowledge has become more exact as to the etiology and natural history of most diseases, and because we have acquired a number of methods and tests which we now utilize as indicators of health and disease. Notwithstanding this general advance in knowledge, accurate diagnosis seems to be less common than in days gone by, because, it may be, that in our eagerness to apply the *indicators* we forget to study *the whole individual* By such study I mean the securing and utilizing of all available information as data for diagnosis In our zeal to apply modern methods and tests, which are indeed but a part of the physical examination, we are apt to fail to go further and adequately consider the other essentials underlying accuracy in diagnosis

We have only to remember how the early clinical recognition of pulmonary tuberculosis was impeded for a number of years following the discovery of the tubercle bacillus, and how com-

pletely we are now dominated by the presence or the absence of a Wassermann reaction when we think of the possibility of a syphilitic infection, or with what confidence we resort to the Roentgen ray for diagnosis even in common gastro-intestinal conditions All such methods, to which the phrase "indicators of health and disease" might well be applied, are invaluable aids, but they should be utilized as aids and not as "short cuts" to diagnosis There is both time and place for the *application* of laboratory methods They should be used for the purpose of securing further and supplemental evidence, but never to supplant one's clinical observations, the use of one's senses and reasoning powers

The way to accurate diagnosis is beset with many difficulties, one of which is lack of thoroughness on the part of the physician Medical education is partly to blame for lack of thoroughness How can the physician be thorough in his work if his Alma Mater has failed to give him proper opportunity for proper equipment? Notwithstanding the difference in training among physicians, if the physician, whatever his primary medical education may have been, would give to each individual the best that is in him, accurate diagnoses would be far more common than they are today

To get anything worth while we must have desire backed up by effort It is natural for human beings to go in the direction of the least resistance, and it is probably this tendency in many of us that causes us to fail to give the best that is in us to the sick If we would recognize morbid processes in the living we must overcome this tendency with desire and with effort

Accurate and complete data are the foundations of accurate diagnoses To get complete data takes time and patience, and if they are to be accurate, self-criticism and the critical sense must dominate us and others at every step The sources of the desired data in every case are in the statements of the individual or of his relatives and friends, and in the physical examination

It is not my intention at this time to dwell on the necessity for thoroughness in the physical examination in its broadest sense including as it should, the application of instruments of

precision and the use of all necessary laboratory methods The doing of these things collectively represents but one of the factors tending toward accurate diagnosis, but I cannot refrain from calling attention to the necessity of enlarging the scope of the physical examination particularly in two diseases, *tuberculosis* and *syphilis*, to the end that every member of the family be studied where one of its members presents evidence of either of these diseases The history of "chronic bronchitis" in the parent may prove on investigation to be tuberculosis, the source of infection in the dyspeptic and neurotic daughter, and the history of rheumatism in the father may prove to be tabes, thus accounting in part for the frequently ailing progeny or the chronic invalidism in the mother

Thus, enlarging the scope of our physical examination in many instances will not only render our diagnosis more certain in the individual, but will also enable us more surely to practice preventive medicine But diagnosis has to do essentially with the individual, the study of him, of all that he is The individual is a product of two great factors, his antecedents, which we call heredity, and his reactions to his ever-varying environment These are the other factors underlying accuracy in diagnosis to which I desire particularly, yet briefly, to direct attention at this time Representing by 100 per cent all the factors underlying accuracy in clinical diagnosis, those of heredity and environment have a value of 70 per cent , at least, in most cases

1 **The Factor of Heredity** —One of the headings to be found in a well-balanced clinical study is that of family history An account of the disease incidence in the parents, in their brothers and sisters, and in the brothers and sisters of the individual, is there recorded with more or less completeness We thus recognize the importance of the data afforded by the factor of heredity, yet the details are often meager, probably for the reason that many of us fail to realize the wealth of information to be derived by a careful elicitation of the family history

It is common to note in case descriptions in medical meetings and in current literature that the family history is negative,

negligible or unimportant, when, as a matter of fact, the *negative*, *negligible*, or *unimportant* family history does not exist It is always important because, first, it discloses either health or disease tendencies, second, the manner in which it is given affords information concerning the intelligence, education, and mental state of the individual, third, it may yield information having a definite bearing on the present illness, fourth, it may disclose hereditable disease (cancer, optic atrophy, deafness, certain forms of ataxia, tremors, muscular atrophies, hemophilia, etc), or a congenital disease (syphilis), or the possibility of the effects of a germ plasm poison (syphilis, alcohol, metallic poisons, etc)

With all these possibilities in mind, surely no one could find a case wherein study of the family history might be called "negligible" or "unimportant" All the reasons just given for a careful consideration of the family history are obvious and require at this time no further comment In order, however, that all available information may be secured it is necessary that some regular outline be followed, noting particularly, if living, the disease incidence and age, and if dead, age, cause and year of death, in the parents, uncles, aunts, brothers, and sisters in chronologic order It is important to note the time of death of near relations, because it will be frequently found that such occurrences so lower the resistance of the individual as to precipitate or complicate his present trouble

Family pride and ignorance often prevent the individual giving accurate information concerning the disease incidence and cause of death in near relatives The "pneumonia" or "bronchitis" which will be admitted must often be interpreted as pulmonary tuberculosis, sudden death, a suicide, nervous prostration, a definite mental disease, nervous spells, epilepsy, chronic rheumatism, tabetic pains, etc It requires the use of much tact and critical sense to secure an accurate family history, but it is of such importance in diagnosis that the physician who takes the time will be amply rewarded for his effort Remembering that the information secured about the family is at best hear-say testimony, often made doubtful either by pride or ignorance, the

physician's critical sense should cause him when in doubt to verify the statements concerning the "good health" of relations by questioning the neighbors and, when possible, by personal inspection

Such intensive studies of family histories as are here implied, will reveal to the physician the dominating factor of heredity as a factor in both health and disease, and, moreover, a pathology which eludes all other methods of research—a pathology which is of the "warp and woof" of the individual

2 The Factor of the Individual's Reactions to His Environment.—The quality of the individual's reactions to his environment, even his length of life, is in some way dependent on the quality of the germ plasm from which he developed This is a biologic fact of great importance and it finds constant application in clinical medicine The quality of the germ plasms is indicated by his family history, and it is further indicated by his personal history Modern studies of heredity show beyond question that the germ plasm from which the individual develops contains the potentialities (determiners) which make for health or disease in him, as well as for his success or failure in life If this be true, all things being equal, it must follow that, to be healthy, to be useful, and to live long is not so much dependent on our environment as it is on our inherent ability to react in a favorable manner to it

In saying this, however it is not implied that to be "well born" means everything and that environment means nothing in the life of an individual Some of us less fortunate in the choice (?) of our progenitors though handicapped may still lead relatively healthful and useful lives by careful and intelligent adjustment to our environment But one is less able than another to make adjustments or to react in a favorable manner to environment, one is more vulnerable, more susceptible to disease than another and these are fundamental differences in the individuals of the species As physicians we must recognize differences in individuals, in their health and disease tendencies Hence, knowledge of the environment and the manner in which the individual has reacted to it is an important factor under-

lying accuracy in diagnosis This factor is to be found in the personal, commonly called past, history of the individual, and it should embrace all available information concerning (*a*) The health of parents at the time of conception and the health of the mother during gestation (*b*) The manner of birth—normal, prolonged, or instrumental (*c*) Nutritional conditions during early years of life and since then (*d*) The menstrual history in females and of the periods in pubescence and climacteric in males as well as females (*e*) The disease incidence in chronologic order, specifying the diseases, their duration and sequelæ, remembering that it is a waste of energy to write such a phrase as "the usual diseases of childhood" (*f*) The incidence of accidents and injuries in chronologic order (*g*) The sex and venereal history—the time of awakening of the sexual instincts, their gratification or suppression the sexual habits in males and females, the date and duration of each attack of gonorrhea and its complications "In what year did you have a sore?" or "When did you have a sore?" are questions not so likely to be evaded, as to ask bluntly "When did you have," or "Have you ever had, syphilis?" The sore being admitted, questions concerning incubation and subsequent history will help to form conclusions as to the probable nature of the lesion (*h*) The opportunity for education, the years in school and the grades attained (*i*) The past and present occupation and the hygienic surroundings and associations incident to each (*j*) Home environment, remembering that it is not only the housing but likewise the associations in the house which make either for health or disease (*k*) The habits in the use of tea, coffee, alcohol tobacco, drugs, specifying the quantity in each, and then, to get at the truth in some individuals, it is often necessary to use a multipher from 2 to 6 Moreover, the habits and interests in life, such as church, social work, recreation, sports, bathing, bowel function food, sleep, are all matters of medical inquiry (*l*) Marital history, age of husband and wife at the time of marriage and health of consort since then, the date and product of each pregnancy, noting the age and state of health the age date and cause of death of each child in chronologic order

It does not seem necessary to discuss the value of the several lines of inquiry just mentioned The bearing which former illnesses, accidents, occupations, and habits may have on the present illness is appreciated and given more or less complete consideration by most physicians, but the mental reactions of the individual to his environment are appreciated by few It is in the investigation of this phase of the personal history that the clue to diagnosis in many functional conditions can alone be found Some one has said "Treat the patient as well as his disease," and this might well be paraphrased "Diagnose the patient as well as his disease" This cannot be done if we fail to study his mental, as well as his physical, reactions to his environment To be of the greatest value in diagnosis the personal history must be investigated from every point of view The same may be said of the family history, the history of the present illness, and of the physical examination It is through these avenues of investigation, watching his step at every turn, that the physician must pass on his way toward accuracy in clinical diagnosis

CLINIC OF DR JOHN ZAHORSKY

BETHESDA HOSPITAL

THE ZED REACTION IN INANITION

FOR many years I have been interested in a singular group of symptoms which appear in the majority of cases of partial or complete starvation whenever the starved condition is relieved The most striking instances of this kind occur in cases of pyloric stenosis of young infants a short time after the pyloric stenosis is opened, but the symptoms also occur in other forms of inanition, *e g*, after prolonged feeding with cereal decoctions and other foods which are deficient in protein content and caloric value It is a common manifestation in marasmus (athrepsia)

For this group of symptoms I propose the name of the Zed reaction, since it is undoubtedly advantageous for study and discussion of any subject to have a distinct name Why use the term "Zed reaction"? The name Zed is an old name for the letter Z Here it means nothing, except that it designates a final reaction before recovery

The Symptoms —The infant is suffering from a pyloric stenosis or other condition which prevents an adequate amount of food from entering the intestine He loses in weight over a period of many days The symptoms of inanition appear pallor, cold extremities, sunken fontanel, hollow eyes, flabbiness of the tissues, slowing of the pulse, subnormal temperature, anuria, and constipation

The stenosis is relieved and the proper quantity of food is administered The Zed reaction appears.

The Zed reaction is characterized by a slight gain in weight, an elevation of temperature, and the appearance of watery stools

The reaction may be slight, it may be so severe as to end in death

The tendency to diarrhea after a pyloric stenosis is relieved is generally appreciated Many authors in describing the treatment after the Rammstedt operation warn us that the feeding must be carefully supervised "There is a great tendency to looseness of the bowels after operation" (Ashby)

To this diarrheal tendency generally recognized I desire to add two other symptoms a gain in weight and a slight elevation in the temperature The syndrome is not complete, however, without a laboratory finding—the watery stools contain a large number of cells

The Zed reaction is an inflammatory condition of the intestinal mucosa occurring in infants previously starved after proper feeding is instituted, and is characterized by a gain in weight, slight elevation in temperature, and a watery nature of the stools, which contain a large number of cells

Having lost a few babies from diarrhea following the operation of pyloric stenosis, I took great care in feeding these infants mothers' milk only, and in very slowly increasing quantities It made no difference how carefully the feeding was carried out, this diarrheal tendency almost invariably was manifest

A study of the stools microscopically revealed a great discharge of cells—columnar epithelium, lymphocytes, leukocytes, and lymphoid cells These fill the fluid part of stool or are embedded in shreds of mucus Many times clumps of degenerated leukocytes (pus-cells) were observed

Analysis of the Symptoms —The gain in weight may be only slight It is not a slight gain caused by the accumulation of water in a dehydrated baby, it suggests at least an increase in the blood volume The lips and skin appear more rosy and the extremities feel warmer

The elevation in temperature is usually slight (1 or 2 degrees) and its duration is one or two days only Sometimes irregular elevations occur for several days Secondary elevations a week or more after the primary rise have been observed The pulse becomes accelerated

The diarrhea may be slight or very severe depending in a great measure on the quantity of food ingested Even careful feeding of mothers' milk on a maintenance ration produces three to five watery stools daily When artificial food is given the stools may be increased to twenty or more Often there is a marked loss in weight during this period and the baby may succumb

The stool microscopically contains undigested curds or flakes suspended in a watery fluid The color varies from yellow to green Gradually this consistency increases and a normal stool is found after several days In severe cases the fluid nature of the stool may persist for two weeks, with frequent relapses after recovery

Pathogenesis —It is generally supposed that this diarrheal tendency is a functional disturbance, induced by the weakened condition of the bowels Too much food is given and a fermentative diarrhea supervenes This weakened condition of the digestive tract after starvation is well known This functional inefficiency has been attributed to a weakness from non-use More definite is the explanation proposed by Marriott and others that the blood volume is reduced and the intestine does not receive sufficient blood to discharge its normal function

I studied the stools in these cases by the technic detailed elsewhere It was found that this diarrhea was associated with a discharge of many cells The first day only a few would be encountered leukocytes and lymphoid cells A few days later the appearance under the microscope was that of pus The watery part of the fluid was crowded with degenerated epithelium, lymphoid cells leukocytes Gradually these lessened, and with the disappearance of the cells the nutritive condition of the baby rapidly improved The conclusion was inevitable that some kind of inflammatory condition of the bowel was a part of the Zed reaction

Mucosal Contamination —I venture to offer the following explanation and introduce another term, "mucosal contamination"

During the period of semistarvation the mucous membrane

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A study of the stools microscopically revealed a great discharge of cells—columnar epithelium, lymphocytes, leukocytes, and lymphoid cells These fill the fluid part of stool or are embedded in shreds of mucus Many times clumps of degenerated leukocytes (pus-cells) were observed

Analysis of the Symptoms—The gain in weight may be only slight It is not a slight gain caused by the accumulation of water in a dehydrated baby, it suggests at least an increase in the blood volume The lips and skin appear more rosy and the extremities feel warmer

The elevation in temperature is usually slight (1 or 2 degrees) and its duration is one or two days only Sometimes irregular elevations occur for several days Secondary elevations a week or more after the primary rise have been observed The pulse becomes accelerated

The diarrhea may be slight or very severe, depending in a great measure on the quantity of food ingested Even careful feeding of mothers' milk on a maintenance ration produces three to five watery stools daily When artificial food is given the stools may be increased to twenty or more Often there is a marked loss in weight during this period, and the baby may succumb

The stool microscopically contains undigested curds or flakes suspended in a watery fluid The color varies from yellow to green Gradually this consistency increases and a normal stool is found after several days In severe cases the fluid nature of the stool may persist for two weeks, with frequent relapses after recovery

Pathogenesis —It is generally supposed that this diarrheal tendency is a functional disturbance, induced by the weakened condition of the bowels Too much food is given and a fermentative diarrhea supervenes This weakened condition of the digestive tract after starvation is well known This functional inefficiency has been attributed to a weakness from non-use More definite is the explanation proposed by Marriott and others that the blood volume is reduced and the intestine does not receive sufficient blood to discharge its normal function

I studied the stools in these cases by the technic detailed elsewhere It was found that this diarrhea was associated with a discharge of many cells The first day only a few would be encountered, leukocytes and lymphoid cells A few days later the appearance under the muscroscope was that of pus The watery part of the fluid was crowded with degenerated epithelium, lymphoid cells leukocytes Gradually these lessened, and with the disappearance of the cells the nutritive condition of the baby rapidly improved The conclusion was inevitable that some kind of inflammatory condition of the bowel was a part of the Zed reaction

Mucosal Contamination —I venture to offer the following explanation and introduce another term, "mucosal contamination"

During the period of semistarvation the mucous membrane

cannot properly cleanse itself The diminished secretion and peristalsis permits the accumulation of food residues, bacteria, and dead epithelial cells in the multitudinous crypts and between the villi The lessened blood-supply also diminishes cellular resistance and the normal or abnormal bacteria in the intestine penetrate the submucosa and are held in the lymph-follicles As soon as normal peristalsis is established and the blood-supply augmented, the mucosa undergoes an inflammatory change and cleanses itself Peristalsis is increased, more juices are poured out, the food is hurried on more rapidly, more food reaches the colon and undergoes fermentative changes At the same time many solitary follicles swell, burst, and discharge cells and bacteria into the lumen of the intestine After this cleansing process digestion and nutrition become normal

The cause of the Zed reaction is a cleansing process following a severe mucosal contamination The severity of the reaction depends on many factors, the chief of which are the extent of the contamination, the number and virulence of the bacteria which have penetrated the columnar lining, and the resistance of the infant Too much undigested food by its own fermentative products will, of course, aggravate the symptoms

Summary.—The name Zed reaction is proposed for a syndrome characterized by fever and diarrhea following inanition, when the food supply is increased It occurs very typically after the operation for pyloric stenosis Evidence is offered to show that this is a true inflammatory reaction A theory of mucosal contamination is suggested as a most reasonable explanation

I will now present a case and will show you several clinical charts of other cases

Case I—E M , a boy, was first seen when five weeks old He is the firstborn, of healthy parents Weight at birth 7½ pounds He was born at term after a rather long but normal labor Nothing was observed wrong with the baby after birth There were no attacks of cyanosis and no convulsive seizures, took the breast eagerly and normal lactation was established

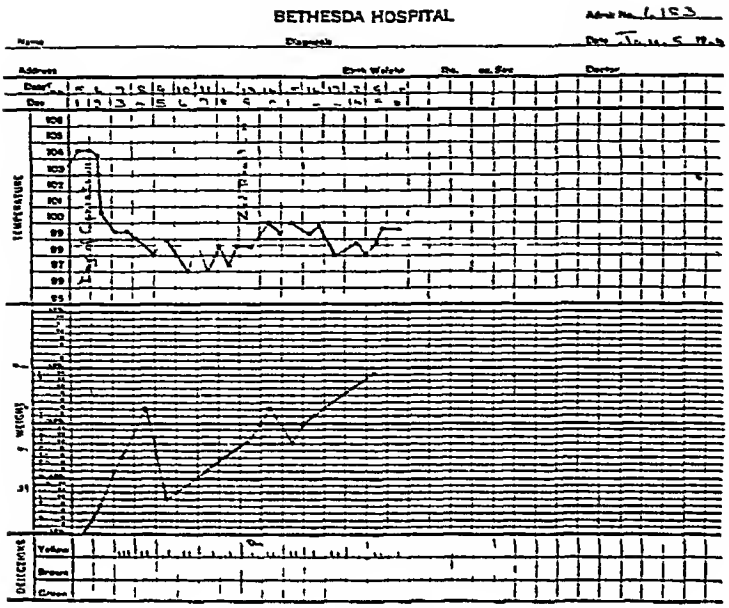

Fig 49.—Zed reaction ninth to tenth day after operation

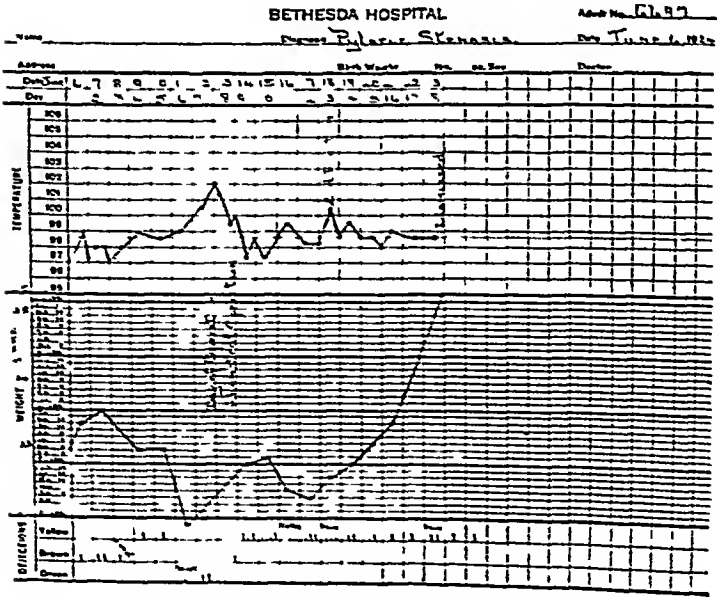

Fig 50.—Zed reaction five days after operation.

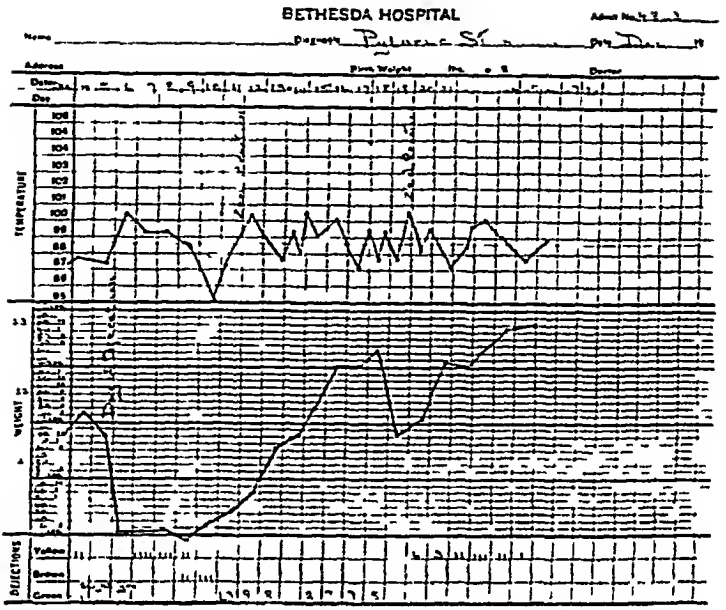

Fig 51 —Zed reaction very severe Began on the sixth day after operation Persisted for two weeks or more The loss in weight on the 18th was due to a great reduction in food

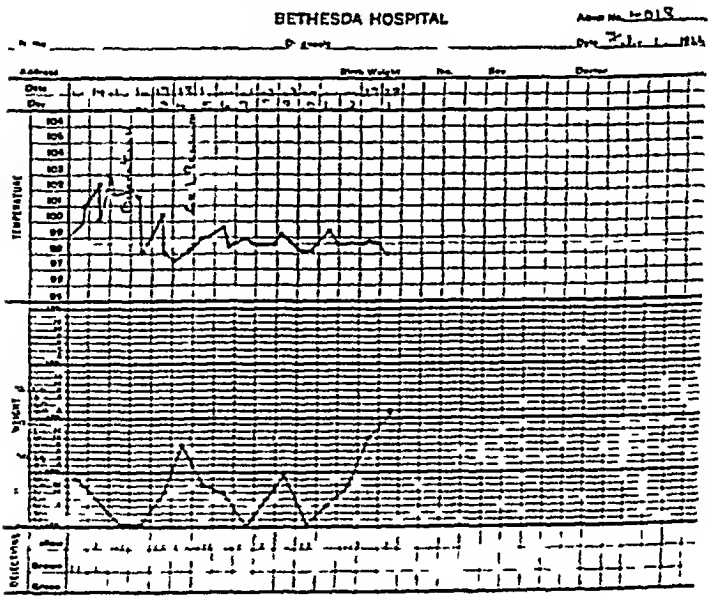

Fig 52 —Zed reaction three days after operation

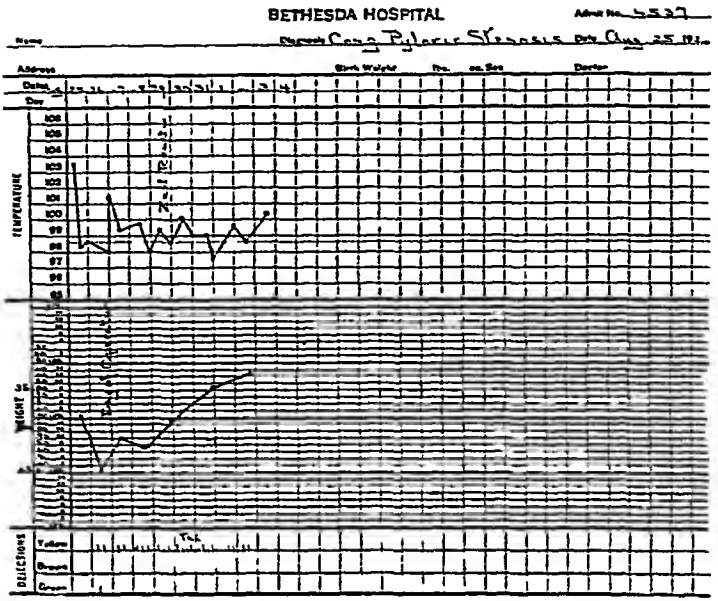

Fig 53 —Zed reaction three days after operation

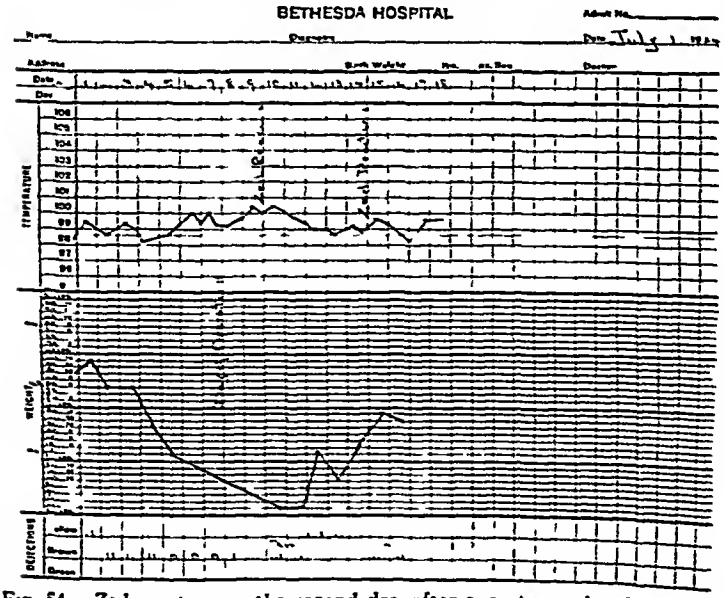

Fig 54 —Zed reaction on the second day after operation Another reaction five days later

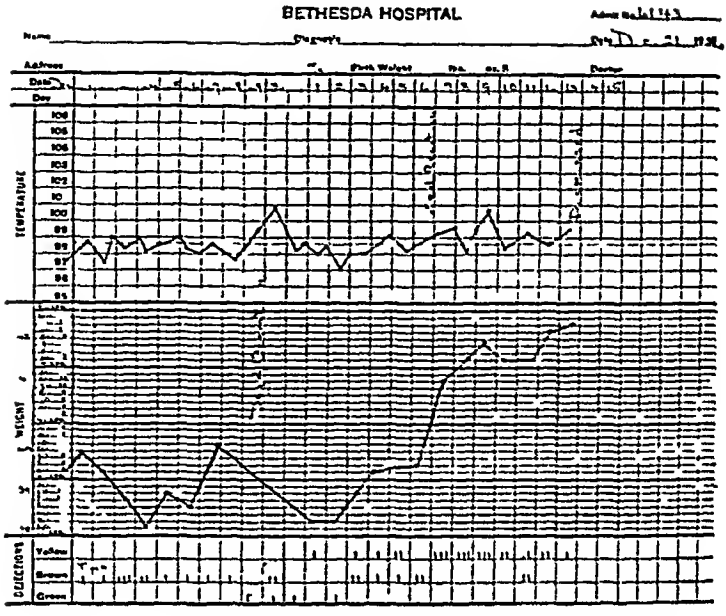

Fig 55 —Zed reaction eight days after operation

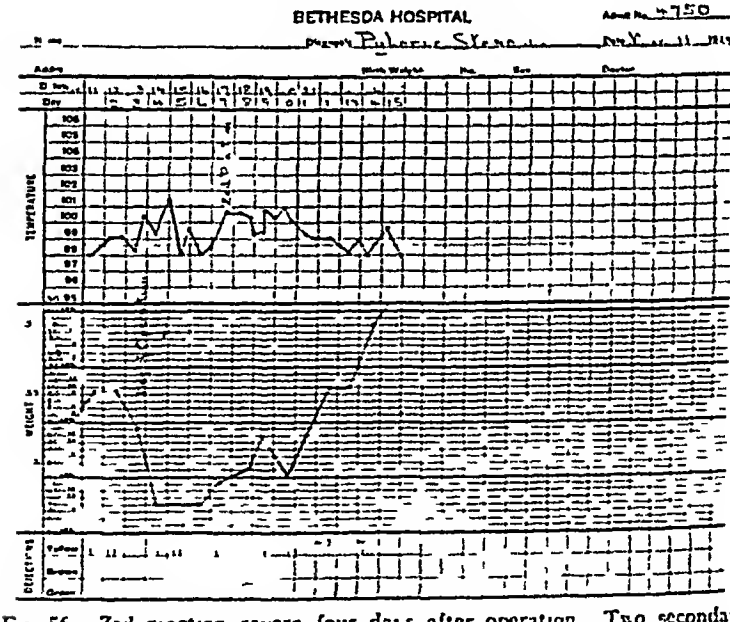

Fig 56 —Zed reaction, severe, four days after operation Two secondary reactions

after three days When he was two weeks old he began to spit up his food excessively Some simple measures employed to stop this seemed unsuccessful When three weeks old he began to vomit forcibly The mother describes the typical projectile vomiting This vomiting has increased He seems to vomit more than he has nursed at times, for the mother observed that at times he has just commenced to nurse when a large amount of milk would be ejected with great force Five days ago he was

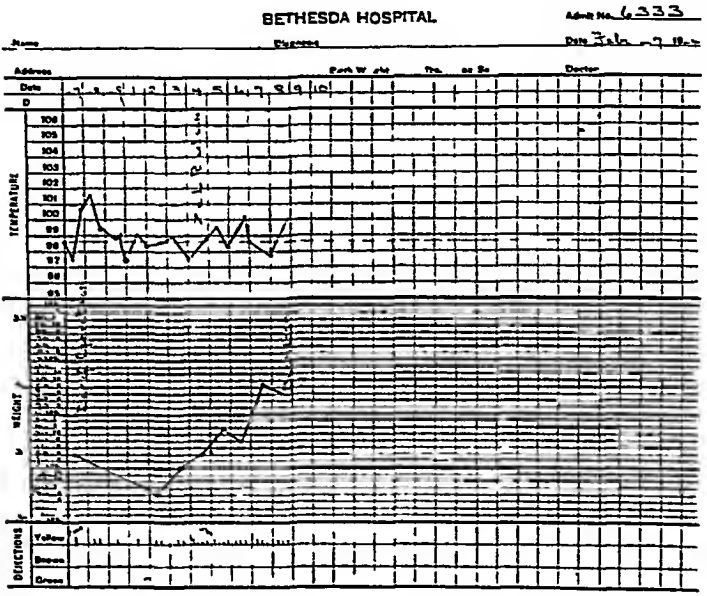

Fig 57 —Pyloric stenosis Zed reaction on the third, fourth, and fifth days

placed on condensed milk, but there has been no improvement. He has lost in weight the last two weeks and weighs just the same as at birth He has passed very little urine for several days The bowels are constipated He seems very hungry all the time and takes food or water eagerly He has no cold, coryza, or febrile disturbance

Examination —Thin, atrophic baby The skin feels dry, but the tissues are elastic Nothing abnormal is discovered on

examination of the head throat, and chest The movement of the extremities seem normal

The abdomen is distended over the upper half, and the flanks and lower abdomen are flat Enormous and vigorous peristaltic waves are easily detected over the gastric region, no pyloric tumor was palpable at the time, but this was made out when the baby was under an anesthetic before the operation

The baby was sent to the Bethesda Hospital Tests were made to determine to what extent the stomach was capable of emptying itself The stomach was washed out with ½ per cent of sodium bicarbonate solution and 3 ounces of dry milk diluted was introduced by the stomach-tube Three hours later reintroduction of the stomach-tube yielded almost the whole amount of milk It was found on several tests that the residue was invariably at least three-fourths of the milk ingested

An attempt was made to overcome the pyloric stenosis by means of thick cereal feeding and the administration of atropin, but after six days' trial the conclusion was reached that the baby was losing in weight too rapidly to delay operation

Operation by Dr Roland Hill A typical tumor was found Operation according to the method of Rammstedt

Ringer's solution had been injected, 1 ounce in each axillary space, daily This was repeated before and after operation Only breast milk was fed, in gradually increasing doses

On the second day after the operation the baby began to have thin watery stools The first day no pus-cells were found It is now the fifth day after the operation, the baby has gained in weight, but the stools continue frequent and watery One drop of the freshly drawn stool is thoroughly mixed with a drop of water on a slide You will observe that the fluid contains a very large number of leukocytes and lymphoid cells, 100 or more to the field

(The infant continued to do well, but even after ten days pus-cells were still found in the stools)

That the intestine easily becomes infected under conditions which lead to imperfect nutrition has been shown experimentally by McGarrison It may be an inadequate supply of protein

that is, the nutritive ratio of the food is too broad; or there is a deficiency of vitamins or there is actual starvation In any of these conditions the intestine gradually loses the power of cleansing itself and saprophytic and pathogenic bacteria proliferate and penetrate the protecting epithelial lining Hence, it is possible to foretell the appearance of an inflammatory reaction in many cases of simple malnutrition inanition, and marasmus This inflammatory reaction in the end is salutary, although during its progress it may be exceedingly dangerous to the life of the infant

This enteritis following states of malnutrition or starvation, as soon as an adequate supply of food is administered, I call the Zed reaction It is characterized by the syndrome—rise in the temperature, a gain in weight diarrheal stools and the appearance of numerous cells in the fecal matter I desire to present to you such a case

Case II—F S girl four months old, was brought here because she has not gained in weight She was born somewhat prematurely, weight at birth 5½ pounds There has been no indication of hereditary syphilis The parents seem healthy The baby was nursed for a few weeks and then the breast feeding was supplemented by condensed milk and malted milk Then she was placed on Mellin's Food and condensed milk, which caused a slight diarrhea Then she was given malted milk, 2 teaspoonfuls to 5 ounces, and also nursed the breast three times a day She was seen first at this time The stools were still thin but contained very few cells

A complemental feeding of barley-water was ordered at this time The diarrheal condition promptly subsided—weight 9 pounds As the baby clearly had not been fed a sufficient amount of protein for several weeks, powdered protein milk was added to the barley-water This brought about an immediate gain in weight, but also produced a diarrhea The weight rose to 9½ pounds and a week later to 10¼ pounds During all this time the baby had four to six watery stools daily The stool freshly drawn from the rectum is thin and under the microscope contains a large number of cells

I will relate the history of another case in which the symptoms were much more violent

Case III—C W, girl, three months old, gives a history of having had recurring digestive disturbances ever since birth She was nursed at the breast for three weeks only but because the baby did not thrive, she was placed on various artificial foods It was clear that the baby was starving most of the time Highly diluted milk mixtures, cereal decoctions, and proprietary foods formed her principal rations

Attempts to place her on cow's milk invariably resulted in a severe digestive disturbance

The baby when first seen weighed only 8 pounds and presented the typical picture of marasmus, she was placed on a buttermilk mixture and the caloric value of the food rapidly increased In two days she began to gain in weight, her skin became warmer, and the lips became rosy On the third day a slight fever developed, which was followed by a violent diarrhea The stools were thin, slimy, and soon became loaded with pus-cells Under the microscope leukocytes and lymphoid cells were closely crowded together as in solid pus This enteritis lasted two weeks, and during this time we were compelled to feed the baby a minimum diet, but she ultimately recovered

These cases are presented to illustrate the assertion made before that the Zed reaction occurs in a variety of nutritional disorders and is a manifestation of resistance on the part of the intestine, and not, as is commonly taught, merely an evidence of overfeeding or overstepping the threshold of food tolerance

I will go still further In the literature we find many references to such phenomena that have been called buttermilk fever, protein fever, and gastro-enteric or alimentary intoxication I am convinced that many of these fevers are really manifestations of the Zed reaction, that is, an infectious or inflammatory reaction of the intestine when an adequate supply of food is administered, and thereby the blood-volume is increased

You may well ask, How does the Zed reaction differ from an ordinary infectious diarrhea? The answer is that there is little

difference in the symptoms, but in infectious diarrhea there has been introduced into the intestinal canal a virulent pathogenic micro-organism, as the dysentery bacillus In the Zed reaction the bacteria normally present in the intestinal canal, and harmless in health, have penetrated the mucous membrane and must be expelled before the intestine can regain its proper function The reactions are similar, but in one the healthy infant may be attacked, in the other only the poorly nourished baby will be affected

The practical lesson to be drawn from this study is this· whenever the Zed reaction appears, do not assume that the infant does not tolerate the food and immediately place it on a starvation diet You must continue to feed the baby a maintenance or an optimum ration with plenty of protein until this intestinal inflammation subsides Many a baby is starved to death because we assume it is intolerant to food, when, as a matter of fact, it is merely cleaning up a mucosal contamination Pay little attention to this mucopurulent discharge, it must go on until the intestines are cleaned Check the peristalsis by medicines (paregoric, bismuth, tannin), but do not starve the baby It is only by feeding them and keeping up an increasing blood-volume that the intestines can be restored to health

CLINIC OF DR H W SOPER

St Luke's Hospital

THE DIETETIC MANAGEMENT OF CARDIOVASCULAR RENAL DISEASE

The dietetic treatment of cardiovascular renal disease has been largely empirical However, ever since the discovery of albumin in the urine physicians have entertained the notion that meat and eggs are not good foods for nephritics I will not attempt here to present the voluminous literature pertaining to the low-protein diet

Salt-free Diet —The *salt-free diet* appears to have been first advocated by Widal and his co-workers, who demonstrated the rôle played by chlorid retention in the production of edema In Germany the work of the French school, headed by Widal, was confirmed by Bayer,[1] However, considerable opposition to the theory is observed in German literature Widal[2] presented a complete study of the pathologic physiology of edema, hydration, and albuminuria in parenchymatous nephritis He is a warm advocate of chlorid restriction in treatment Croftan[3] in 1912 pointed out the efficacy of a salt-free diet in the treatment of edema

The most comprehensive study of the treatment of arterial hypertension by salt-free diet is the paper by Frederick M Allen[4] appearing in 1920 He reports great benefit in properly selected cases of hypertension by sharply limiting the salt intake He believes that salt restriction may be of great value in cases of general arteriosclerosis, *i c*, its continued use as a prophylactic measure He points out the fact that many oculists are of the opinion that some cases of retinitis are due largely to sodium

chlorid retention Allen discusses the difficulty in arranging a diet sufficiently poor in salt which at the same time is reasonably satisfying to the patient

Konikow and Smith[5] report good results in the use of salt-free diet in the reduction of arterial hypertension

James P O'Hare[6] studied 18 cases of vascular hypertension Only 2 cases showed improvement sufficient to compensate for the difficulty in carrying out the treatment He believes it cannot be carried out except in the hospital

Motzfeldt[7] reports very good therapeutic results in the use of salt-free diet, but warns against its indiscriminate use He believes in strict adherence to the functional tests, with dietetic restrictions to conform to the individual conditions at the time

Rabinowitch and Childs[8] recently reported a very interesting case of chronic nephritis associated with chronic nephrosis, in which the salt and protein restriction did not remove the edema In this case a high-protein diet produced removal of the edema, with improvement in the clinical picture as well as in the blood and renal functional tests

Joseph L Miller[9] studied the elimination of the chlorids in nephritis, with the following conclusions "In patients with moderately severe nephritis associated with edema the ingestion of large amounts of sodium chlorid is followed by a chlorid retention The patient gains in weight, the edema becomes more marked, the albuminuria increases, and symptoms may develop resembling uremia In patients with very severe nephritis, and especially those with uremia, chlorid retention is very marked, as scarcely any of the extra chlorid administered is eliminated In individuals with apparently healthy kidneys following the ingestion of sodium chlorid there is a chlorid retention equal to that of mild nephritis The individual gains in weight, but there is no visible edema, no albuminuria, and no uremic symptoms"

A complete review of the literature is out of place in this article In general, writers on this subject agree as to the restriction of salt and protein in the treatment of edema While

there is disagreement in the use of these agents in the treatment of arterial hypertension, my observation is that internists will use salt restriction and low-protein diets in decompensation, but do not continue it after the edema has disappeared

A most important and valuable contribution to the subject of diet in nephritis was made in 1923 by Sansum [10] He studied the chemical composition of foods and classified them as to their systemic acid values I reproduce his tables as follows·

ACIDITY OF CERTAIN FOODS PER 100 GRAMS

Bread, white	2 7
Bread, whole wheat	3 0
Corn, sweet, dried	5 95
Crackers	7 81
Cranberries*	
Eggs	11 10
Egg-white	5 24
Egg-yolk	26 69
Fish	
Haddock	16 07
Pike	11 81
Meat	
Beef, lean	13 91
Chicken	17 01
Frog	10 36
Pork, lean	11 87
Rabbit	14 80
Veal	13 52
Oysters	30 00
Oatmeal	12 93
Peanuts	3 9
Prunes, plums*	
Rice	8 1

*The ash of these foods is alkaline, but because of contained substances which form hippuric acid in the body they increase the acidity of the urine

ALKALI-PRODUCING FOODS PER 100 GRAMS

Almonds	12 38
Apples	3 76*
Asparagus	81
Bananas	5 50*
Beans	
Dried	23 87
Lima, dried	41 65
Beets	10 86
Cabbage	4 34
Cauliflower	5 33
Carrots	10 82
Celery	7 78
Chestnuts	7 42
Currants, dried	5 97
Lemons	5 45
Lettuce	7 37
Milk cows	2 37
Muskmelon	7 47*
Oranges	5 61*
Peaches	5 01
Peas, dried	7 07
Potatoes	7 19*
Radishes	2 87
Raisins	23 68
Turnips	2 68

*These foods have been found experimentally to be very efficient in reducing the acidity of the body

The *neutral foods* are butter, cornstarch cream, lard, sugar, and tapioca

Sansum notes the acidity of the urine and modifies the diet accordingly He reports great improvement in cases of arterial hypertension, with falling blood-pressure and reduction of albumin in the urine of 90 per cent of the patients treated He points out that many of the so-called "normal diets" contain a large proportion of acid-forming foods This may be a factor in the etiology of blood-vessel damage

It is highly probable that the good effect of a milk diet is not merely due to the low-salt content, but to the fact that milk is an alkali-producing food We must remember that, as Allen particularly emphasized milk contains too large a percentage of

sodium chlorid for a strictly salt-free diet, that other foods should be selected in the severe cases of edema

Personal Experience—We[11] have used the low-protein diet for years in the treatment of arterial hypertension, also the salt-free diet in decompensation and edema from other causes Recently we have utilized the principles laid down by Sansum in the formulation of our dietaries The following is our standard diet for the ambulant hypertension patient

All vegetables
All fruits, both cooked and raw
Four glasses of sweet milk a day
All nuts, except peanuts
Drink water freely
Use sugar in moderation
Use no salt
Use no vinegar Use lemon juice freely
Olive oil
Use butter (salt free) in vegetables
Dates, figs, raisins

There is nothing said about the quantity for the patient to use on this list except for the limitation to 4 glasses of milk a day (about 32 grams of protein) Additions and corrections are made, based on the reaction experienced by the patient Often the first addition will be in the use of bread baked without salt *

While many difficulties are presented in the preparation of a salt-free diet, we have found it possible to carry it out both at home and in the hospital A frequent source of error is in the use of canned vegetables, all of which contain a large percentage of salt as do all bread-stuffs, including cakes and all crackers on the market except those mentioned below As a substitute for salt we have been using sodium citrate as originally recommended by Masci[12] Many patients object to the taste of the citrate Therefore I have modified it by the addition of 1 dram

* In this connection the Kosher-Biscuit, put up by the Loose-Wiles Biscuit Company, is salt free, and Triscuits, made by Shredded Wheat Biscuit Company, are free from salt or any other chemical agent Johnson Educator Food Company puts out an excellent salt-free wafer

of sodium bromid to the ounce of citrate The average patient will consume about 1 ounce of the mixture in one week's time Therefore the quantity of bromid consumed is probably negligible The "salt" is used by the patient at table and not in cooking Of course its use is restricted to the ambulant patient and is not used in the stage of edema or decompensation

I will now present a list of cases which are selected to portray the various conditions in which dietary measures are indicated The case records are abstracted in brief You must assume that all of them were carefully studied, as reference will not be made to detailed findings I will further add that the cases presented do not include our failures—which, of course, formed a small percentage of the totals The late Dr John T Hodgen said many years ago that he reported only his failures, inasmuch as they were more instructive than the successful cases, but in these days of therapeutic (particularly dietetic) nihilism we may be pardoned for selecting our successes

Case I—Male, aged sixty-one Valvular heart lesion, decompensation, and general edema Entered hospital in January, 1923 Dyspnea very severe Unable to sit up Blood-pressure 155/115 Before coming to the city his physician had been giving him large doses of digitalis Was extremely nauseated Four ounces of fermented milk (Bulgarian culture) was given every two hours Water restricted to 4 ounces every two hours Morphin and atropin hypodermically The edema disappeared rapidly Salt-free and low-protein diet was continued until he left the hospital, March, 1923 He has been kept under observation to the present time Relapses when he gets away from his diet list, but is adhering strictly to it now

Case II.—Male, aged sixty-two Terminal cardiovascular renal condition A point of great interest in this case is that he needed no more digitalis after the beginning of dietetic treatment He had taken it almost continuously for one year Entered the hospital May, 1922 Has been water-logged for past six months, despite the continuous use of digitalis Liver was very large

and hard Unable to lie down because of extreme dyspnea. Urine was loaded with albumin and contained many hyaline and granular casts Blood-pressure 168/100 His diet consisted of 6 ounces of milk and cream every two hours, and 6 ounces of water every two hours, given at regular intervals Salt-free foods were gradually added The edema disappeared rapidly He left the hospital in June, 1922 He has adhered strictly to the salt-free diet since leaving the hospital He is kept under observation and has never had any break in compensation or required digitalis He is active and performs all his business duties as usual He has no difficulty whatsoever in following the salt-free diet He stated that the flavor of food is much better without the addition of salt and he has no desire whatsoever for it His urine is free from all trace of albumin and casts and his functional tests are all within the normal limits

Case III—Male, aged sixty-four Valvular lesion heart, nephritis, and arteriosclerosis Was seen in consultation with Dr Wm Engelbach in October, 1921 He had a tremendous break in compensation, severe dyspnea, and general edema. Digitalis has lost its effect on him On the Karell diet he finally pulled through the attack He had another break in November, 1923 and was sent to St Luke's Hospital He responded very nicely to the strictly salt-free low-protein diet and left the hospital in February, 1924 The diet was extremely irksome, and he finally made up his mind that anything was preferable to such a régime He had no taste for vegetables and fruits, but craved meats and rich, highly spiced salty foods He had repeated breaks in compensation, all responding beautifully to salt and protein restrictions Finally he died of apoplectic stroke on February 20, 1924

Case IV—Male, aged sixty-four Valvular lesion heart Occupation, farmer Entered St Luke's Hospital in March, 1922, with a severe form of decompensation Blood-pressure was 158/128 NPN, 44 per cent PSP, 30 per cent He did not respond well to the Karell diet It was necessary to give

him large doses of digitalis and he had considerable nausea After being under treatment for two weeks' time he developed a severe acidosis which finally responded to carbohydrate feeding and glucose and sodium citrate proctoclysis He has been kept under observation since leaving the hospital up to the present time and has had no further breaks in compensation and has not required the use of digitalis He adheres to a salt-free and low-protein diet

Case V—Male, aged sixty-eight Double aortic valvular lesion and nephritis Came under observation in 1915 Seen in consultation with Dr A E Taussig He responded quite well to low-protein diet without the restriction of salt Since that time he has remained under Dr Taussig's care with moderate restriction of salt and low-protein diet He has required digitalis pretty regularly He had quite a number of breaks in compensation and suffered a great deal from dyspnea I saw him again in consultation with Dr Taussig on November 26, 1924 Had quite a severe break in compensation, dyspnea was very distressing Liver enlarged Edema of lower extremities We put him on fermented milk (Bulgarian culture) for a week and finally built up his diet making it strictly salt free, using the principles laid down by Sansum in his basic diet He improved steadily and has been far more comfortable than he was while under the *moderate* restriction of salt When he feels the deprivation of salt he states that the freedom from distressing symptoms amply compensates him

Case VI—Female, aged sixty-six Severe angina pectoris Seen September 18, 1924 in consultation with Dr Mary McLain and Dr A E Taussig Has been a diabetic for years Her blood-pressure is usually very high No edema Complained a great deal of gas pressure about the heart She was put on a salt-free and basic diet of Sansum and was quite free from her attacks of angina and gas pressure for several weeks Her blood-sugar, however, remained high and we found it necessary to give her insulin She is now quite comfortable under a diet

list consisting of one rather liberal carbohydrate meal daily, preceded by 20 units of insulin Her breakfast and supper are free from carbohydrates The protein in her diet is estimated at 75 grams daily I am now attempting to get her accustomed to the bromid and citrate "salt," thereby reducing her sodium-chlorid intake

Case VII —Female, aged sixty-five Angina pectoris complicated by pernicious anemia with achylia gastrica Entered the hospital October 27, 1924 Seen in consultation with Drs W Baumgarten, A E Taussig and F R Fry Her attacks of angina disappeared under a modified Sansum and salt-free diet Fermented milk and hydrochloric acid have been very useful in her case Her kidney function is good Her attacks of angina began again soon after the addition of flesh food, eggs, or salt to her diet list She is now up and about and is quite comfortable

Case VIII —Male, aged sixty Nephritis of the prostatic obstructive type Seen in consultation with Drs Caulk and Sanford Entered St Luke's March 20, 1924 Heart tremendously enlarged Severe dyspnea with pulmonary edema Liver hard and enlarged NPN, 51, PSP, 5 Was fed milk and cream, 6 ounces, alternating with 6 ounces of orange juice every two hours Salt-free carbohydrates were gradually added Dr Caulk relieved the obstruction by his "Punch" operation He remained on diet with salt restriction and low protein and has completely regained his health

Case IX —Male aged fifty-five Parenchymatous nephritis, tremendous general edema Entered hospital March 16, 1924 All palpable arteries very hard and tortuous No valvular lesion Very high-grade edema of legs and arms Skin broke in several places with oozing of serum Large amount of ascitic fluid Could not take digitalis because of nausea Attempted to give it hypodermically, but skin broke down and had to discontinue it Was kept on Karell diet for one month, when

edema gradually began to subside Finally disappeared altogether Is now at home doing his work as farmer He adheres to a strictly salt-free and low-protein diet

Case X —Male, aged forty Contracted kidney In uremic coma interrupted by convulsions Maniacal delirium when aroused from coma Constant vomiting Urine showed large amount of acetone Was given 1000 c c of intravenous 10 per cent glucose solution daily for four days Levin duodenal catheter was introduced into duodenum and 1000 c c of water and 1000 c c of Bulgarian milk daily by the Murphy drop method He eventually made a complete recovery

Case XI —Male, aged twenty Scarlatinal nephritis Delirious, unable to retain any food Urine very scanty, containing much albumin and acetone Proctoclysis of glucose and sodium bicarbonate A Levin intranasal catheter was introduced into duodenum He was given small quantities of Bulgarian milk, which was gradually increased until 1500 c c were given daily Good recovery

Case XII —Male, aged sixty-three Contracted kidney and arteriosclerosis, angina pectoris, and severe headaches Came under observation in October, 1921 Blood-pressure 194/90 No break in compensation Was put on a low-protein with moderate salt-free restriction Made good improvement, but suffered considerably from rheumatic pains and dull headaches His diet list was changed to Sansum's basic plus strictly salt-free diet in September, 1923 Since that time his rheumatism and headaches have been greatly improved and his blood-pressure has remained around 130/90 He is now quite comfortable and his general state of nutrition is very good His hemoglobin and red cell count are well up to normal

COMMENT AND SUMMARY

Case XII illustrates how the progress of chronic interstitial nephritis and arteriosclerosis may be checked and the patient

made comfortable by dietetic measures Furthermore, it is possible to utilize the principles of a basic salt-free, low-protein diet in the maintenance of a good state of nutrition with normal hemoglobin, without an undue loss of body weight It is always necessary to reduce the weight of the obese patient However, many nephritics gain in weight under dietetic management In this connection butter fat, cream and olive oil, as well as the liberal use of sugar are necessary to secure sufficient daily calories In some quarters one hears criticisms of this strict regimen, based upon the fact that many such patients do not show poor utilization of sodium chlorid by laboratory test However, there comes a time in the progress of the disease when chlorid retention does occur Intelligent prophylactics would seem to indicate that we should attempt to postpone this event and protect the damaged renal tissue by at least a low-salt intake

Many of these cases come to us with severe acidosis Proctoclysis of 3 per cent glucose and 2 per cent sodium citrate solution is very useful The intravenous use of glucose is of great value in the severe cases, 1000 c c of a 10 per cent solution properly sterilized (autoclaved) is allowed to flow in slowly, according to the principles laid down by Woodyatt and Sansum

In the unconscious and delirious patient complete control of the food and fluids may be secured by the Levin gastroduodenal catheter The tube is beautifully adapted to intranasal introduction and readily and quickly finds its way into the duodenum

The use of fluids in decompensation with edema is often a problem In general, fluids must be sharply restricted in the beginning of treatment, gradually increasing as the edema subsides In the prostatic obstructive type of case the fluids must be pushed just as soon as proper drainage has been secured

Perhaps the most difficult problem in dietetics is presented by the patient with the combination of diabetes with valvular heart lesion, nephritis and arteriosclerosis as exemplified in Case VI It would really be impossible to make her comfortable without the use of insulin

When the patient has recovered from the decompensation

and edema, supervision of the diet, introducing the principles of Sansum's basic foods in maintaining blood alkalinity, combined with the reduction of protein and the restriction of salt, will not only tend to prevent the recurrence of attacks, but will materially add to his comfort and well-being

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CLINIC OF DR SIDNEY I SCHWAB

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TRYPARSAMID AND PARESIS

A CLINIC on tryparsamid and paresis seems particularly fitting just now because this drug is to be released for general use by the Rockefeller Institute some time after January 1, 1925 The Neurological Service at Barnes Hospital was selected among others to try out this drug in cases of neurosyphilis for the purpose of studying its therapeutic results, to determine the best method of administering it, and also to study its chief deleterious effect, that is, the production of amblyopia and damage to the optic nerve In this clinic there has been treated with tryparsamid about 200 cases The material includes practically all types of neurosyphilis, with probably a 25 to 30 per cent incidence of paresis I shall select from this group 5 cases which illustrate the success or failure of this drug in order to give a kind of cross-section view of tryparsamid as far as paresis is concerned

Before doing this it is important to consider paresis as a clinical entity and to determine just what is meant by this term and what its clinical and pathologic implications may be There still exists a deal of confusion in the published reports about paresis depending apparently upon whether a neurologist, surgeon, dermatologist, or genito-urinary specialist is reporting his results For some curious reason this typical primary and most common psychosis appears to excite the therapeutic enthusiasm of all sorts of men for whom mental diseases admittedly is not only a closed book, but a subject that arouses not a bit of interest or concern Therefore, the conception of what a case of paresis is remains a matter of considerable doubt, and many of the published reported cases diagnosed as paresis are probably not paresis at all

Paresis must be viewed in at least two ways The first is concerned with the histologic reaction of the nervous and general system resulting from the invasion of the organism of syphilis, second, the reaction of the individual in point of conduct, behavior, intelligence, content of consciousness, etc , plus the defect of the central nervous system as a consequence of the histologic changes produced When these things are given due consideration, and if they reasonably can be explained to be the result of the anatomic changes assumed to be present, then the diagnostic pathway toward paresis is opened Supporting evidence is to be found in the examination of the blood and spinal fluid, furnishing accumulative evidence in support of the diagnosis of syphilis of the nervous system I should like once more to emphasize at this point that all the data determined from the serologic and microscopic examination of the blood and spinal fluid support or confirm a diagnosis of syphilis, and do not, except in an indirect fashion, reveal whether paresis is present or not A paretic colloidal-gold type curve in the spinal fluid by no manner of means justifies the diagnostic conclusion of paresis, nor is its absence a determining factor in excluding this diagnosis

The thing that causes the changes in the brain and especially certain parts of the brain in paresis is the entrance and the permanent habitat of nests of spirochetes in the deeper lying tissues of the cortex and subcortex How they get there and why they penetrate and how they maintain themselves are matters of speculation at the present time The reaction of the tissues to this type of invasion has now been studied in a sufficient number of cases to be fairly well understood

The final and permanent changes in the cortex, especially in individuals who have had the disease a long time are the results of an inflammatory and circulatory process which is set up through the presence of spirochetes in the central nervous system, and, in particular, their entrance and permanent habitation in the gray matter of the cortex The gross appearance of such a brain shows marked evidence of a chronic process of this sort The convolutions, particularly in the frontal, prefrontal, and parietal regions are flattened smaller than normal, and

often of a pale grayish appearance Areas of softening and tissue disintegration can be made out, the results of old and recent hemorrhages can be seen which through organization gives the appearance of pachymeningitis hæmorrhagica The white matter of the brain is sometimes soft and edematous, the ventricles may be dilated and granular, the weight of the brain is diminished as a whole Microscopic study of the cortex shows a venous stasis, arterial wall changes, meningeal thickening, and tissue disintegration The most common lesion is a pia arachnoid infiltration of plasma-cells There are lymphocytes and marked perivascular infiltration Small vessels are often occluded, and typical arterial wall degeneration resembling in every way syphilitic vessel sclerosis are made out

The neuronic system as a whole shows atrophy, degeneration, and complete disappearance of the cell, axis-cylinder, and dendrites This change is particularly seen in the tangential and the supra- and infraradial fibers Nerve-cells are often completely destroyed, altered in their appearance, and displaced. There is a marked decrease in the number of dendrites and nerve-cells show all varieties of degeneration, in the supra- and granular layers of the cortex very little normal tissue is found There is also a great increase of neuroglia fibers and cells The whole upper cortical pattern is sometimes so altered that the individual layers cannot be made out It can be seen from this description that the changes produced in the upper layers of the cortex, particularly in the frontal, parietal, and motor regions of the brain, explain the various clinical symptoms due to the involvement of those portions of the cortex which have to do with motor activities, speech, and the higher intellectual activities The temporary paralysis, speech defect, convulsions, tremors, and muscular insufficiency are direct results of active or subactive processes in the region of the cortex which control these functions Of interest from the standpoint of effective treatment is the fact that so many of the changes that have been described are necessarily permanent in character, and if a return of function is to be interpreted as a result of tryparsamid treatment, then the fact must be recognized that some other portion of the cortex which

has not been injured is capable of establishing the functions that have been destroyed The irregularity in localization of the process and the tendency to scattering give an opportunity, of course, for those portions which are not destroyed to function with a fair degree of activity Inasmuch as the changes are probably primarily vascular and are of the nature of an inflammatory reaction, complete restitution is possible in such areas as have not undergone permanent destruction As far as can be determined the spirochetal nests are too removed and isolated and apparently too well protected to be influenced directly by any treatment at the present time available The question of the activity of the cortical spirochetal nests is at the present time unanswered Perhaps owing to their position deep in the cortical layers they may be regarded as less active and destructive than would otherwise be the case The exact relation between the spirochete nests and the changes that have been described has not been worked out Enough can be gathered, therefore, from the description of the pathology of paresis to indicate how closely the relation between pathologic changes and the production of clinical symptoms in this particular disease is

In view of the character of the changes found in paresis and considering the remote chance that a preparation such as tryparsamid could reach the spirochetal nests in any effective manner, the question is raised as to its therapeutic theory Tryparsamid is not experimentally a spirocheticide, therefore, even if its penetration was such that it could reach the deep-seated organisms, it would be as ineffective there as it was shown to be in test-tube experiments Tryparsamid is an effective drug because in some way, not understood at present, it serves to intensify tissue defenses and stimulates the cell to a more vigorous resistance to spirochetal intoxication

The clinical diagnosis of paresis is based upon the study of three sets of factors and observations The first is the presence of signs and findings, clearly determined by direct and objective examination, which point directly to the conclusion that the central nervous system has been damaged as a result of syphilis Second, a study and analysis of the intellectual assets of the pa-

tient at the time of the examination to determine whether there is present at the time of the examination mental defects of a type that are associated with cortical changes characteristic of paresis This has to do with tests devised to find out how much a patient knows about himself and his affairs, how clearly he is in touch with his surroundings, how much he appreciates the every-day circumstances in which he lives, how much insight he has in regard to his present condition, how he fits into his environment, how well he can conduct his business and social affairs, and how far away he is from his former cultural level Efforts must be directed toward a study of his personality, of his manners of his finer ethical qualities of his tastes and appreciations, and all elements that form the sum total of his make-up In the study under this second category come tests in regard to memory, orientation, judgment, concentration, attention, imagination, and other intellectual elements of this sort—emotion, inhibition, false and erroneous ideas, delusions, and abnormal sensory reactions Under the third category would come a careful scrutiny of the patient's past history as far as it is associated with the beginnings of the mental changes, and a comparison of this present state as far as social business life are concerned with what they were before the patient became a subject of psychiatric scrutiny The sources of information which come under the last category are to be obtained from a study of his home conditions and surroundings, his business and social life outside, and the various activities in his particular environment These are ordinarily not the subject of careful scrutiny in the course of a general physical and neurologic examination It is only by assembling information of this sort and analyzing it that a definite conclusion in regard to the type of mental deterioration characteristic of paresis can be obtained It is clear that a diagnosis of paresis can be finally determined only after a very thorough and painstaking investigation of the individual

Of particular importance is the tendency of this disease to pass through intermissions These seem to bear no necessary relation to treatment It is necessary to study in a state of intermission data of the sort referred to for the purpose of decid-

ing whether the intermission is a return toward the normal, or is, in fact, a period during which the patient is really his normal self again There is a great deal of loose therapeutic conclusions found scattered in recent literature on the treatment of paresis where the assertion is made that the patient has regained his former personal qualities and is physically and intellectually as good as he ever was It is questionable whether a paretic, in view of the nature of the pathologic changes present in the brain, can ever be so fully restored that no mental defects are ascertainable, and for this reason many of the optimistic reports in the tryparsamid literature should be viewed with a degree of skepticism

When the clinical diagnosis of paresis has been reached through consideration of the data under these three headings, then the serologic and microscopic results of the examination of the blood and spinal fluid are to be considered, and if they show the usual changes associated with syphilis of the nervous system, then these facts can be used as supporting evidence for the diagnosis of paresis If they are absent, however, the diagnosis of paresis must stand or fall upon the basis of the facts obtained in the examination under the categories that have been mentioned

The question of interpreting negative findings in spinal fluid and blood is important because tryparsamid can cause the Wassermann reaction in both spinal fluid and blood to become negative and can flatten out the typical paretic curve These do not mean that the paretic reactions on the part of the brain have been necessarily brought to a standstill, but simply that the evidence of an active response of the central nervous system to the spirochetal infection has disappeared Other methods of treatment than tryparsamid have in some instances produced equally notable changes in the spinal fluid and blood, so that response to treatment must be considered in the final interpretation of atypical findings in blood and fluid The final therapeutic test of a paretic must, however, be placed upon another basis entirely, and that is the study of the individual from the standpoint of his conduct, behavior, and the other elements

which go to make up what may be briefly called here his intelligence It is thus a matter of much study extending over a long period of time before a final conclusion as to the efficacy of tryparsamid in the treatment of paresis can be obtained

The method of giving tryparsamid to cases of suspected or proved paresis has now been more or less simplified and standardized, at least in the material from which these cases have been selected After the patient has been examined, preferably in a hospital, and a diagnosis of paresis has been made, then the plan of treatment is more or less as follows A moderate dose of tryparsamid is given according to the standard body weight of the patient This averages between 2 and 4 grams On alternate weeks salvarsan is also given The usual course is about seven to ten weeks, with the tryparsamid one week and the salvarsan the other During the intervals between the tryparsamid and the salvarsan the patient is given from two to three deep injections of mercury intramuscularly At the end of the first course of treatment the patient is allowed to leave the clinic and rest for from one to two months At the end of this time, when a restudy of the spinal fluid and blood have been made, a second course is carried out, then a third and fourth, as the case may be During the whole period of tryparsamid treatment there is a careful examination of the eye-grounds and visual fields made from time to time in order to determine the existence of amblyopia or optic nerve changes, either or both of which appear in about 10 or 15 per cent of all the cases If the patient with suspected paresis has ocular changes or definite evidence of optic neuritis or atrophy, then the tryparsamid must be given in smaller doses with longer periods of rest and more careful scrutiny of the patient In practically all cases in which amblyopia has been present it is only a temporary reaction, and in the absence of pre-existing optic neuritis or atrophy there has been no case in which permanent optic nerve changes have resulted

In presenting this series of cases it will be possible only to give a brief sketch or summary, because the essential detailed study will take entirely too much time Therefore it is well to

note that the summary has been made from a consideration of the completed data which have previously been alluded to

Case I —This is a man forty-one years of age, single, who says he is a salesman by occupation As a matter of fact he has chiefly been employed in clerical positions in hotels On entrance the patient's statement is that he has no trouble of any kind, that he comes into the hospital for treatment to prevent any come-back of syphilis The chief item of the past history is chancre at twenty years of age This was incompletely treated even according to the standards then in vogue Up to three or four years ago he drank considerable, but of late has not The present illness dated from some time during the summer of 1922 Before that he was doing very well, making a good living, and apparently had saved considerable money He began work at the age of eighteen in a hotel, and in this business he has continued ever since In his last place he worked ten years, he averaged about $300 a month in wages, and at times, owing to special opportunities, a great deal more than that He admits that he lived a fast life, had loose morals, drank, and had much to do with women According to the statement of both this patient and his sister he was suddenly "fired" from his position in the hotel, and immediately went to Oklahoma Here the continuity of his jobs was broken and he had one job after another, losing each one on account of his inability to remember things, lack of judgment, and general want of business sense He also lost his money, had to sell his jewels and other private possessions, and finally decided to come back to St Louis He drove his car back from Oklahoma and found, to his surprise, that he had a great difficulty in remembering the road and directions He became so perplexed about 20 miles outside of St Louis that he determined to leave his car in a garage In St Louis, although this had been his home for a long time, he could not find his way about the streets, and wandered aimlessly until he was picked up and his family notified He was then taken to a physician, who gave him salvarsan and mercury After that he was sent to the City Sanitarium, where he spent one year

His account of that year shows that he was chiefly employed in ward duties and he was given the task of taking care, as far as he was able to do so, of some of his fellow-paretics In these cases he saw evidence of insanity which he was quite sure he himself did not have In the hospital he was quiet and orderly, but lacked energy, interest or understanding He presented the picture of a depressed, dull, and hopeless individual At the end of the year he was taken home, where he remained until brought to the Barnes Hospital At home he was quite reserved and seemingly satisfied He never left the house and came to be regarded rather as a child that needed watching and care He was very much surprised when he was informed by his sister that he was about to receive treatment at the Barnes Hospital He believed that he was perfectly well and saw no reason for treatment of any kind, and apparently had lost all ability to measure himself at the present time with what he had been before

On admission it was noted that the patient was very cheerful and optimistic, was somewhat disoriented as to time and place, his memory was found not to be as defective as noted in the history, the general physical examination, except for a degree of obesity, was negative, the neurologic examination showed an ankle-clonus, plus knee-jerks, right greater than left, and Babinski reflexes on the left His blood Wassermann was 3+, his fluid was 4+, globulin increase, 80 lymphocytes, his curve was 5554320000, his disks were hyperemic, but no marked vessel changes This patient was placed upon a course of tryparsamid and salvarsan, beginning with 4 grams of tryparsamid with mercury between He returned to the Barnes Hospital again for treatment and observation about two months later During the interval he has felt very well and now feels fit and has more energy than before His blood Wassermann was then negative He was admitted to the Barnes Hospital a month after this His blood was found to be negative, spinal fluid shows marked improvement, the curve is flattened out, and there are now no important evidences of syphilis of the nervous system as far as spinal fluid and blood are concerned He is taking long walks alone, and apparently has no trouble of any kind, and as far as

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one can see he appears to be perfectly normal A recent note from his sister, with whom he lives, is to the effect that he has changed altogether for the better, takes a great deal of responsibility, is quite careful about his personal appearance and what he says and does, and is saving his money, is working hard, and seems to be getting along very well As far as his sister can notice he is living a very moral and careful life, his only recreation seems to be going to the moving pictures occasionally, and he usually goes alone His sister and other members of the family are encouraged about him

In this case there is a very evident improvement as the result of tryparsamid The improvement is not only seen in the improved physical appearance of the patient, in his conduct and behavior, but also supported by the fact that the evidence of syphilis of the nervous system has largely disappeared from his blood and spinal fluid The most striking thing about this case is that he has resumed his old employment, that he has managed to keep the position for some months, that he is working hard, and is evidently able to handle himself as a normal individual Here again the question of intermission or improvement comes up, and it is only by long-continued observation that this point, as far as this case is concerned, can be settled

Case II —This is a man fifty-four years of age, a salesman and merchant by occupation, whose paresis was ushered in in the stormy fashion of a convulsion For some time previous to April 7, 1924 it was noticed by his family, friends, and business acquaintances that he was less efficient in his work, lacked his usual energy and ability, had periods when he seemed to lose track of things It was noted also that his memory was defective, especially in regard to the names of his customers, he began to be less prompt at appointments, and there seemed generally a change in his personal characteristics, particularly so far as business matters were concerned He left his business and went to Europe for a rest While in London and on his way home he had two or three very violent convulsions which were thought to be epileptic A few days after coming back to St Louis he

was found completely unconscious in bed, with his tongue bitten, and other evidences of a violent convulsion He could not be aroused from his stupor and was taken to a hospital in that condition It was there that I first saw him in consultation with his family physician A diagnosis of apoplexy had been previously made, but no evidence pointing to a lesion of this kind could be discovered A consideration of the past history suggested that the convulsions were of the type usually seen in paresis due to the changes in the brain cortex, such as have been pointed out The blood and fluid both showed a markedly positive Wasserman and numerous lymphocytes in the spinal fluid, as well as a very marked paretic curve Although the convulsions were not repeated, the state of stupor continued, and he was sent to a neighboring sanitarium for treatment Examination at the hospital and subsequently showed a constantly high blood-pressure generally around 200 systolic, over 120 diastolic Other significant data are myopic pupils with reactionless right pupil and slight reaction to light in left pupil, irregular outlines, a slight difference in size of pupils, a fine tremor in both hands, lips, and tongue The rest of the physical examination was largely normal, an occasional trace of albumin, and one or two fine hyaline casts were found from time to time in the urine The most persistent findings were the constant high blood-pressure and the evidences of syphilis of the nervous system which have been alluded to

He was given a series of deep injections of mercury together with tryparsamid and salvarsan at weekly intervals After two or three weeks he began to show remarkable improvement mentally, and his speech, which before was slurring and difficult to understand, began to be clear again, the tremor of the fingers and hands disappeared, and he was able before he left the sanitarium to write a letter without marked defects in handwriting or in spelling or in the formation of sentences The salvarsan and tryparsamid was kept up with periods of rest between the various courses of from one to two or three months You see this patient now after three complete series of such treatments have been given The change in his mental condition is very

striking When he was first under treatment he was difficult to manage or control, was very restless, continually moving about, and very much worried about himself He presented a picture more of an agitated type of depression than that of paresis, with expansiveness and euphoria He has always had, after he recovered from his stupor, a definite idea of what his sickness was, and often referred to his previous infection of syphilis and blamed himself for his present condition During the early period he was much given to emotional attacks of crying and weeping, bemoaning his fate, and speaking of the unfortunate state in which he was in At the present time, with a fair degree of realization of what his disease is, he is not showing any unusual emotional reactions, but rather thinks sensibly about it, regarding treatment as a possible release and being unusually cooperative and obedient His memory for names and recent events is still defective, although he is able with some effort to give a fair account of his recent movements He is particularly accurate in his recollection of events and circumstances that happened some years ago, and is able to recount in great detail where he was and what he was doing at periods anywhere from fifteen up to three years before his present illness In spite of his defective memory and his inability to perform simple tests in regard to dates and places, he is able to write a letter remarkably free from errors, both in spelling and composition He is, on the whole, subdued and easily managed, obeying the rules and regulations that have been devised for him, and trying in every way to aid his physicians in carrying out instructions His blood Wassermann has shown a tendency to decline, the curve in his fluid has been considerably altered, but the most unusual change has come about in the cell content of the spinal fluid, which has now been reduced to under 12 cells There has been some fluctuation in the Wassermann reaction in his fluid, but, on the whole, it has remained unaltered in a permanent fashion Blood-pressure has shown no tendency to change in any way

This case is noteworthy on account of the stormy beginning, the fact that this patient was rapidly approaching a condition of acute dementia, a patient whose conduct was such that he had to

be sent to a sanitarium a paretic whose insight into his condition at first was completely nil and at the present time is acute and logical and who has so changed under treatment that he is able to be at home, take care of himself as an ordinary man might, come to the office for treatment as required, and is willing and able to understand medical directions, tremor has largely disappeared, speech is no longer slurring, and whose handwriting is apparently as good as it ever was He has, however, at present defective memory and a lack of self-control in face of emergencies or important business affairs which would not permit him to resume his former employment

Case III —This patient is a woman fifty-six years of age, a widow She was brought into the hospital because she was nervous, for some time had difficulty in talking, often being unable to say and sometimes even to think of the word she wanted to express The husband of this patient had been dead for a number of years, the nature of the disease from which he had died is unknown She has one son, an active and successful young business man Patient had no unusual illness, certainly none that would seem to have any relation to the present condition She had a number of attacks of acute articular rheumatism, the only trace of which is a persistent systolic murmur, the slightly hypertrophied heart of a mitral insufficiency This woman had been unusually active, living with a relative, she had taken charge completely of her own affairs and had up to the present illness managed her modest income with a great deal of insight and care She did sewing, from which she supplemented her income This she did because she enjoyed doing it rather than because it was necessary Until about one year before her entrance into the hospital nothing was noted out of the way. When she was visiting a relative out of town it was noted that she had some difficulty in walking, a tendency to uncertain gait, and found it particularly difficult to go up and down stairs At night she would stumble and for some time she insisted on having a light in her room or wherever it was that she might have to walk in the dark At that time, that is, about a year ago, it

was also noted that she had some speech difficulty, that she did not write as clearly as she did before Specimens of letters which she had written to her son at that time showed that words were often misspelt, that letters were left out of words, and that sentences were begun and not finished

She objected very much to going into the hospital, saying there was nothing wrong with her at all, but finally she was persuaded to enter the hospital for examination On entrance she appeared anxious, apprehensive, restless, and unco-operative She frequently gave way to emotional excesses, crying, and exclaiming that she did not want to stay there, that she was perfectly well She was with difficulty persuaded that she needed treatment The most important facts in the neurologic examination were the presence of obvious speech defects, very small and irregular pupil, slight pupil difference, and limitation in the excursion and direct light Her deep reflexes were found to be increased, but there were no pathologic variations, the gait was unsteady and ataxic, so much so that she would sometimes stumble and fall, and in attempting to get out of bed she would frequently have to be helped and supported The blood Wassermann was found to be 4+ as well as the spinal fluid There were 2 cells in the spinal fluid and an almost typical paretic type of curves A more careful scrutiny of her mentality and her intelligence showed that although the patient was fairly well orientated at entrance, she had marked memory defects except for recent events She often would laugh very loud and long over questions that were asked her, and then respond with some degree of accuracy to them The tendency to laugh and become hilarious was in striking contrast to the periods of depression, during which she would cry and bemoan her fate, believing that she was being persecuted and held in the hospital against her wishes At other times her behavior was care free, euphoric, and rather hilarious She would sometimes laugh apparently at nothing at all for many minutes, and either was unwilling or unable to tell why she felt so happy or at what she was laughing Although she had been at high school for two years she was quite unable to meet the simple tests based on that school level Her

judgment was markedly defective and she was emotionally unstable The formal intelligence tests, therefore, showed a very definite and marked mental deterioration, scattered in distribution, with marked emotional instability, and an utter incapacity to appreciate her present condition—the type of deterioration which is seen very often in the intelligence curves of paretics The patient was regarded then as a case of paresis of rather acute onset, showing evidence of syphilis of the nervous system, presenting a typical mental deterioration of that disease She was given preliminary treatment of deep injections of mercury, seven doses of tryparsamid, and three doses of neosalvarsan During this period of treatment, which lasted something like fifteen weeks, she had various periods during which the paretic process seemed to advance into acute stages For some days at a time she was stuporous, immovable, and stationary, without environmental reactions of any kind, with slow pulse and respiration In such periods it was necessary to feed her through a tube Such stuporous periods would be succeeded by some days of almost maniacal excitement, during which she became noisy and dirty, in and out of her bed all the time, restless, and hard to manage Her speech during such excited periods seemed to improve in remarkable fashion, she was able to say almost anything she wanted to without marked traces of typical speech defect which she at first presented It was impossible, however, to follow the thread of her conversation, as she would go from one subject to another, her sentences were jumbled, and words used without proper significance and meaning In these excited periods she was completely disorientated, recognizing neither the physician, nurse, nor her son Marked hallucinatory episodes marked some of these periods, particularly that of hearing, although there were occasionally visual hallucination also She reacted toward these hallucinations in a more or less logical fashion, particularly those of visual variety A marked delusional and persecutory tendency was also evident, consisting chiefly of the idea that she was being persecuted by her son and kept in the hospital for his own designs In some of the periods she related delusional and phantastic experiences of the past, many of them of the sort that

did not fit in with the kind of life she had always led She would recount in great detail drinking experiences and midnight revels in places where she had never been

After the first few treatments of tryparsamid she had a very marked and interesting lucid period during which her memory seemed to improve, her physical condition also, and her speech In this period she wrote letters to her son which showed little defect of any kind, and in an interview with him on one of his visits she seemed very much like her old self This apparent remission period was the high point in her treatment with tryparsamid in the hospital, and at the end of three months or so it was seen that no important improvement had taken place, that her condition was such that she could not be kept in the Barnes Hospital She was therefore sent to a sanitarium in the neighborhood of St Louis During this period her blood was persistently negative, while the spinal fluid Wassermann decreased until it was scarcely 2+ There never was an increase in cells over the first admission, and on two occasions the paretic curve was completely changed into that of one of low syphilitic meningitic variety, and one apparently quite normal toward the end of the stay at the hospital The spinal fluid again showed a typical paretic curve, although the Wassermann reaction never reached its entrance positiveness For the first few months at the sanitarium she steadily sank into a deep paretic state, totally oblivious of her surroundings, listless, and uninterested, careless of her clothes, often needing feeding In the last week or so a striking change toward a remissive period has taken place Her speech has improved, she is well oriented, recognizes people about her, and presents the identical appearance that she did at the first admission to the hospital A second course of tryparsamid was given after she left the hospital, but since has been discontinued, as the condition seems to be without permanent change or tendency toward improvement This case illustrates a rather typical paresis in an individual over fifty years of age in whom the onset was acute and the progress of the disease very rapid, and in whom two remissive periods in the course of a few months have been reached During such periods the physical

and mental improvement has been so remarkable that complete restitution seemed a possibility In spite of this the disease has shown a steadily progressive tendency, especially in view of the marked defects in the refined qualities of personality characteristics of this type of woman

Case IV —This case is selected because it illustrates a remarkable improvement in conduct in a paretic whose initial responses to the disease were such as to make him a difficult subject for hospital treatment

A man thirty-four years of age, machinist by trade, was sent into the hospital because his wife had noticed that he was becoming what she called "absent minded" and forgetful He had done no work for four months preceding his admission On examination he was found to be a remarkably cheerful person, robust and vigorous looking, smiling or grinning all the time, speaking with a jerking staccato and slurring speech, constantly interrupted by silly and causeless laughter He said that nothing worried him, that he was going to buy a new car, and that he was going to be a chiropractor and make a great deal of money He was particularly energetic in stating that he felt very well, never had been sick, and was in the hospital for a short rest on account of overworking When told that he had not worked for many months he would laugh and disregard the discrepancy with easy nonchalance

Examination showed speech defect, tremulous and uncertain handwriting, tremor of tongue and hands, increased deep reflexes, irregular and slightly unequal pupils, L P showed 80 lymphocytes, increased globulin, 4+ Wassermann and a curve of 1112220000, blood Wassermann was likewise positive He was put upon tryparsamid, beginning with 2 grains, then 3, and mercury with alternate salvarsan

During his first period in the hospital he was difficult to manage and control He wandered about the corridors, he was up at all hours of the night in and out of patients' rooms, disturbing people at work, and making a great nuisance of himself His conduct is best described as silly and childish There were

a number of episodes at this time which illustrate lack of judgment and defects in personal relationship and loss of personal responsibility The fact that he was in a hospital where there were sick people did not seem to enter his mind He was unable to connect his various conduct disorders with the possible bad effect upon others Social sensibility was completely wanting He was dirty and careless in his personal habits, his room was messy, the bed and floor covered with paper, torn bits of pages from books, cigarette stubs, pieces of candy, and food In spite of efforts on the part of nurses to prevent it, nothing could be done to influence a change of habits This was in marked contrast to his usual characteristic, which was that of an unusually neat and careful person At one time he set his bed on fire, which he said was done as a joke

After five doses of tryparsamid and salvarsan he came back to the service on November 9th At this time he was oriented, careful and neat in his personal appearance, and was easily taken care of in the general ward L P showed 6 cells, positive Wassermann, with a curve of 2224567000 His conduct in the ward was that of a perfectly normal patient He read most of the time, was very ready and eager to assist the nurses and orderlies, became interested in the other patients, sat and talked with them, and tried to help in every possible way Insight was remarkably clear and steady, he knew he had been seriously ill, realized that he was suffering from the effects of syphilis on his nervous system The grandiose ideas had completely vanished and his memory was returning, picking up events more and more recent He has several times been presented in the clinics and has conducted himself properly You see now that he is a presentable individual, cheerful, but orderly, speaking with only an occasional slight slur in speech, showing good orientation, and proper appreciation of his surroundings Simple arithmetical tests were answered faultily, however, and other intelligence problems are disappointedly responded to Mental deterioration is evident in spite of an unusual improvement in conduct. If he were measured from the point of view of his former business, that of a skilful machinist, the results would even be more dis-

appointing, He lacks the capacity to put through a task the items of which he remembers and can minutely describe There is here then a change of a fundamental kind in the organization of personality, particularly so in its constructive elements, the "doing" part is severely compromised, when the external aspects have returned almost to their former characteristics

As a tryparsamid effect the improvement is notable, but is limited to what may be described as the ability to maintain his social place in the narrow limits of home

Case V—The last case is that of a laborer, age forty His presenting complaint is nervousness and tremor of the left arm He has been in this hospital on four occasions and you see him now on his most recent admission, having finished his third course of tryparsamid This patient had always been quiet, reserved, and hard working, a skilled laborer, able to do many different kinds of work, always having a job, though changing his work frequently His wife reported that previous to his acute outbreak in August, 1922, she had noticed that he was becoming cross and irritable and often unreasonable in his demands She also noticed that he was dissatisfied with his job, believing he was much too good for it, and saying that that sort of work was beneath him In August of that year, without previous warning, he had some kind of acute attack in which he threatened the people in the boarding house and succeeded in running them out of the house He was violent, abusive, and dangerous He had to be taken to the City Observation Ward where he remained ten days without quieting down to any extent A 4+ blood Wassermann was obtained there He spent the next few months in an institution in the South His mind is a complete blank for this period January, 1924 he entered the neurologic service He had a slurred hesitating speech, but was otherwise alert and co-operative Deep reflexes were very active right patella clonus, myotic pupils irregular in outline Spinal fluid, 30 lymphocytes, 4+ Wassermann and a typical paretic curve

He was put on tryparsamid and salvarsan, and the usual mercury Returning February 19th, his blood was negative, fluid

still plus, with 17 cells On March 20th the paretic curve began to show some change, but the other findings were unaltered In November, after his third tryparsamid series, the curve had become atypical and the cell count was 17 When he left the hospital he said he felt like working and got a job in a machine shop Here he succeeded in injuring his finger and has not worked at a job since His wife noted a great improvement in his conduct at home, he was like his old self, gentle and thoughtful, and has lost his irritability and crossness He is his old self, but seems to lack the initiative to get a job or care much whether he has one or not, he spends his days moping about the house reading all the want ads in the papers, but doing nothing about it He is neat, orderly, and helpful, but seems to have no thought of any other kind of activity or interest but to stay at home and assist in the domestic activities there It is noted by the Social Service worker that he is inclined to use big and unusual words, the meaning of which he does not get He speaks in a formal, stilted, and artificial manner His letters, of which there are examples, are stiff, formal, and grandiloquent He writes a whole page to tell a simple fact or answer a simple question The spelling, however, is correct and sentence formation is good Both talk and letters represent in no way his former and usual personality He seems to be living a part in a play, some one who is austere, very respectable, conventional, and aware of his own supreme importance Many jobs have been obtained for him, but he declines them all, believing they are much beneath him and below what he merits Though he is without funds of any kind, and although he realizes the necessity of working he does not appear to understand the discrepancy in his life—yet he is often depressed at being out of work Memory is defective, but he is not expansive or grandiose

This case shows a definite personality alteration with enough adaptation remaining to enable him to live at home in a fairly normal fashion

These 5 cases are meant to illustrate the average result of tryparsamid treatment in cases of paresis It is obvious that no definite conclusions as to the therapeutic efficacy of tryparsamid

can be made at the present time In view of the experience obtained in the material from which these 5 cases have been selected certain tentative ideas are worth noting Tryparsamid is a drug that must be used with care and careful selection of cases In paresis a study of the type of case and its progress should be made before the drug is given In very advanced cases in which mental deterioration is excessive and where the cerebral tissue degeneration is very evident as measured by symptoms and findings nothing can be expected Optic nerve changes are to be regarded as contraindications for tryparsamid treatment unless the case should seem to promise favorable reaction to the drug In the presence of optic nerve changes in which mental deterioration is not far advanced and in which conduct and behavior are not primarily affected—to such an extent at any rate that adaptation may not be hoped for—tryparsamid may be given in small doses and in lengthened intervals Tryparsamid in association with salvarsan and mercury offers in selected cases and selected types of paresis the most promising method of treatment that is at present available The remarkable changes for the better in conduct and in general physical well-being are evidences of the fact that this drug does exercise a definite influence upon the cellular defensive mechanism In this particular feature it is almost a unique contribution to the pharmacology of syphilitic disease of the nervous system

An attempt has been made in the presentation of these clinical cases to suggest that paresis is largely a matter of abnormal conduct and behavior and that the final diagnostic test should be based upon a study of these abnormal reactions rather than upon any rigid interpretation of the findings in the spinal fluid and blood In this way a clinical estimation of paresis can be built up which has for its purpose the study of the total personality of the patient rather than incidental findings and unimportant symptomatic features

CLINIC OF DR JULES M BRADY

St Ann's Hospital

CISTERNA PUNCTURE IN THE TREATMENT OF HYDROCEPHALUS

The etiology of hydrocephalus is shrouded in mystery and is dependent on many factors

The text-books speak of an external hydrocephalus and internal hydrocephalus

In the former condition, which is unusual, the accumulation of fluid is between the dura and pia and may follow meningeal hemorrhage, pachymeningitis, or any lesion causing cerebral atrophy

Internal hydrocephalus accompanies many different lesions of brain and meninges

The studies of Dandy and Blockfan have shed much light on the condition If the aqueduct of Sylvius leading from the third to fourth ventricle is obstructed from any cause, there will naturally result an accumulation of fluid in the lateral ventricles, as the cerebrospinal fluid is secreted by the choroid plexus

The accumulation of fluid may become so great that in time the cortex may be almost destroyed from pressure The closure of the foraminæ of Magendie and Luschka will bring about a similar picture Various procedures have been suggested, including tapping of the lateral ventricles, with little success Syphilis has long been believed to play an important part in interfering with the proper absorption of cerebrospinal fluid from the subarachnoid space

Recently Marriott has reported success in treating hydrocephalus with diuretin, due to its ability to increase the surface tension of the blood

I was long under the impression that hydrocephalus was absolutely a hopeless condition and impossible of being influenced by any form of treatment

Two successful results in my practice prompt this report

Baby H , seen at seven days of age, with unmistakable evidence of meningeal hemorrhage, there were no convulsions, but symptoms of increased intracranial pressure were quite evident, two cisterna punctures on two successive days liberated a total of 30 c c of black-looking blood Blood to the amount of 60 c c from the father was injected intramuscularly into the baby The result was all that could be desired Twelve days later, the baby having left the hospital, there was definite evidence of enlargement of the head The sutures gaped, fontanel was distended, and the infant was becoming dopey Theobromin was given by mouth in doses of 3 grains three times a day for a period of three days There was no result and the stomach was so upset that vomiting and refusal of food resulted

Cisterna puncture was then resorted to with the withdrawal of 100 c c faintly blood-stained cerebrospinal fluid The baby improved, but four days later the baby's condition seemed worse The head now measured 16 inches Another cisterna puncture was done, with the withdrawal of 240 c c of blood-stained cerebrospinal fluid The bones of the skull collapsed and it was possible to move them about, as though the cranial cavity were empty A wonderful improvement followed, the baby began to take its food better, picked up weight, the head showed no longer any tendency to expand, and now, at seven months, gives promise of making a good recovery The head now measures 18 inches and chest 17½ inches

A case very similar to the above occurred in my practice a number of years ago The boy is now eight years of age and is normal in every way

The cisterna route is chosen for the reason that the fluid in the subarachnoid space is more accessible and for the reason that lumbar puncture in 10 per cent of babies results in a dry tap It is readily understood that this treatment is only of avail when

there is free communication between the ventricles and subarachnoid space

It is an old observation that in hydrothorax withdrawal of some of the fluid frequently results in the complete cure of the condition

We know that intracranial hemorrhage is only diagnosed in a percentage of the cases This is testified to by the number of cases of spastic paralysis seen in the clinic, where the mothers had not even suspected anything wrong at birth

It is entirely possible that an undiagnosed meningeal hemorrhage could be at the bottom of quite a few cases of hydrocephalus, as meningeal hemorrhage is an extremely common condition

The importance of prompt interference in this class of cases cannot be too strongly emphasized A cerebral cortex long exposed to great pressure may be damaged irreparably, as also may changes take place in the cells of the subarachnoid which could not be recovered from

CONCLUSIONS

There is one variety of hydrocephalus which may be completely cured by a free withdrawal of cerebrospinal fluid This may be done most conveniently by puncture of the cisterna magna

It is felt that this type of hydrocephalus is not rare, owing to the frequency of meningeal hemorrhage, which was the cause of the condition in two of my cases

METABOLISM CLINIC OF DR WILLIAM H OLMSTED

BARNES HOSPITAL

INTOXICATION FOLLOWING AMPUTATION IN DIABETES

SINCE the discovery of insulin several cases of diabetic gangrene have come to our attention in which interesting clinical pictures have developed after amputation

Case I —M E W, white woman, age sixty-five

History —Came into hospital because of inflamed right foot Father died of diabetes Scarlet fever and pneumonia as a child, otherwise health has been excellent Two children Sugar was found in urine ten years ago, and during this time has lost weight steadily from 165 to 115 pounds For the past year patient has been taking insulin Physician told her there was only a small amount of sugar in her urine Three months ago began to have pain in right foot, especially in the great and second toes, a crack appeared between the third and fourth toes This crack enlarged and an ulcer formed, which has been growing steadily One year ago patient had an ulcer on the other foot, which healed slowly

Examination —Marked undernutrition (25 pounds) Patient slightly drowsy, but easily aroused Eyes Pupils pin-point Head generally negative, also chest Blood-pressure 170/60 Pulse rapid, varying from 110 to 130, temperature 102° F Abdominal organs not palpable Vaginal-rectal examination showed normal pelvic organs

Right foot greatly swollen, swelling extending to ankle All of the toes are blue and the blue area extends over the entire inner surface of foot Pulsation of dorsalis pedis and posterior tibial arteries could not be felt in either leg

Laboratory—Blood Blood-sugar on admission, 0 374 Leukocytes, 26,000 Plasma bicarbonate, 63 vols per cent Urine showed large amount of sugar Ferric chlorid test faintly positive

Course in Hospital—Amputation of right leg, lower third of femur, was done six hours after admission, by Dr Barney Brooks Dissection of the arteries of the amputated leg showed marked arteriosclerosis with almost complete obliteration of all three major arteries of the leg The temperature was normal the first three days following amputation, although the pulse remained at 100 During the next twenty-two days the temper-

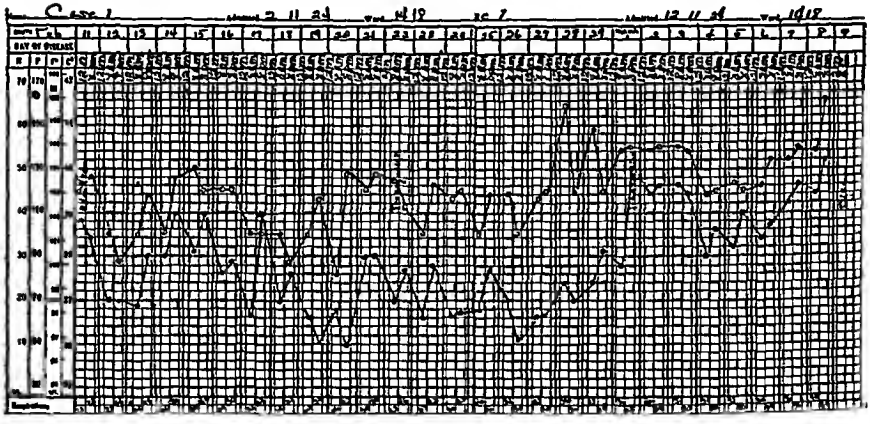

Fig 58

ature varied markedly, ranging from normal to 100° F, and reaching 103° to 104° F three days before death Type of temperature was irregular, not the typical septic course The pulse ranged from 90 to 130, and during the last two weeks never fell below 120

Glycosuria and glycemia were easily controlled with a diet approximating 1400 calories and 50 to 60 units of insulin a day Respiratory rate after operation ranged from 26 to 30 per minute and continued about this rate until the last week of life, when respirations varied between 30 to 40 per minute, and were very shallow in type A week after operation patient became ex-

tremely drowsy, could be aroused only with difficulty There were no signs of meningitis, pneumonia, or other infectious process Eye-grounds appeared the same as before operation Blood-pressure 170/62, heart clear Patient complained constantly of a great deal of pain in the stump of amputated leg Postoperative urine was usually sugar-free, but did show 1½ gm of albumin and many casts, no blood Specific gravity was always high, ranging from 1020 to 1025

For two weeks there appeared to be no change in the amputation stump, all signs of healing were absent, there was no swelling, and no redness There was apparently no blood-flow in the tissues, subcutaneous fat undergoing liquefaction when the sutures were cut and the deep tissues inspected There was no pus, no odor The entire wound had the appearance of tissues completely devoid of blood-supply During the last week of life necrosis occurred in the terminal 2 inches of the stump, and in an area in the internal surface of the stump There was no evidence of infection

Leukocytes, first day after operation, 21,000, polymorphonuclears, 78 per cent At the end of the first postoperative week the leukocytes were 28,000, polymorphonuclears, 86 per cent They then decreased to 20,000 and during the last week of life were 15,000 Four blood-cultures were made, all of which were negative Non-protein nitrogen in the blood, 35 mgm per 100 c c of blood Because of the gradually increasing anemia, the patient was transfused on the tenth postoperative day This was repeated on the twentieth postoperative day Electrocardiograms were essentially normal The general course was steadily downward, the pulse becoming more and more rapid in spite of vigorous stimulation with digifolin and caffein sodium-benzoate and death occurred on the twenty-second postoperative day

The above case was one of typical gangrene with extensive endarteritis of the vessels of the leg There was no inflammation in the amputation stump but, in spite of this, the picture presented was that of septicemia The high fever, rapid pulse rate, rapid, shallow respirations, and polymorphonuclear leukocytosis

gave a picture of intoxication The four blood-cultures were all negative Other interesting symptoms were the gradually increasing anemia, the pin-point pupils and the temporary improvement after transfusion

Permission was obtained for postmortem inspection of the amputated leg This showed a complete necrosis and autolysis of the muscles of the amputated leg as high as Poupart's ligament This necrosis was confirmed by microscopic examination It was further noted that the small sections made in the skin when patient was transfused never healed

What was the cause of this picture of intoxication? It seems most probable that necrosis and autolysis taking place in the amputation stump was responsible for the clinical picture Infection seems to be ruled out because of the absence of any evidence in the organs of the body and in the amputation stump

The observation of the failure of small sections of the skin of the arm to heal, in spite of a very good pulse at wrist, would show that besides a process of diabetic endarteritis there was that second phenomenon seen in diabetes, namely, failure of the tissues to heal, even in the presence of apparently good circulation

Case II—R White woman, age forty-seven

History—Came to hospital because of sore on right foot Inflammatory rheumatism at sixteen Has weighed as much as 210 pounds Gradual loss of weight for past ten years Patient has known for a number of years that she had diabetes, but has never taken care of her diet Five months before coming to hospital patient noticed a slight infection on the fourth toe of right foot This infection gradually became chronic, and there was a slight discharge One month before entering hospital patient painted this infected area with iodin, which apparently made the toe very painful For the past month patient has been in bed

Examination—Weight 169 pounds (25 pounds overweight), rather pale Eyes Pupils pin-point, but react sluggishly to light Head otherwise negative Chest clear, no râles, no

dulness at bases Heart not enlarged, systolic murmur at apex Radial arteries show slight thickening Blood-pressure 140/70 No abdominal organs are palpable Knee-jerks obtained on both sides, ankle-jerks not obtained Dorsalis pedis artery pulsation barely felt on left foot, not on right Neither posterior tibial artery pulsation is felt The skin of the well foot has an ivory color, approaching the color of dead skin, especially when the foot is slightly elevated There is gangrene of first, second, and third toes on right foot, the great toe and little toe being spared The fourth toe is completely black The gangrene extends well up on the dorsum of foot and well back on the sole The black area of gangrene is surrounded by a bluish area of discoloration no blebs

Laboratory—Blood Leukocytes, 19,000, polymorphonuclears, 75 per cent Red blood-cells, 3,900,000, hemoglobin, 85 per cent Wassermann negative Blood-sugar, 0 258 Non-protein nitrogen, 29 mgm Urine Specific gravity, 1019 Large amount of sugar, large amount of albumin, many finely and coarsely granular and hyaline casts, no blood P S, phthalein 15 per cent in two hours

Course in Hospital—Patient was made sugar-free as rapidly as possible with large doses of insulin General condition became worse and the third day after admission amputation of leg in midthigh was performed by Dr A O Fisher Temperature and pulse rate as shown in chart (Fig 59) Respirations varied from 36 to 48, were very rapid and shallow The first postoperative day patient developed moist râles over bases of both lungs, but tubular breathing was never heard Owing to the rapid pulse it was thought probable that the pulmonary signs were due to myocardial weakness Under digitalis and caffein sodium-benzoate therapy the pulmonary condition rapidly improved In spite of the improvement in the lungs the general condition became worse, respirations remained rapid and weak Electrocardiogram showed no signs of myocarditis Leukocytes remained high being 20,000 on the third postoperative day, polymorphonuclears 82 per cent On the fifth postoperative day, leukocytes, 15,000, polymorphonuclears, 83

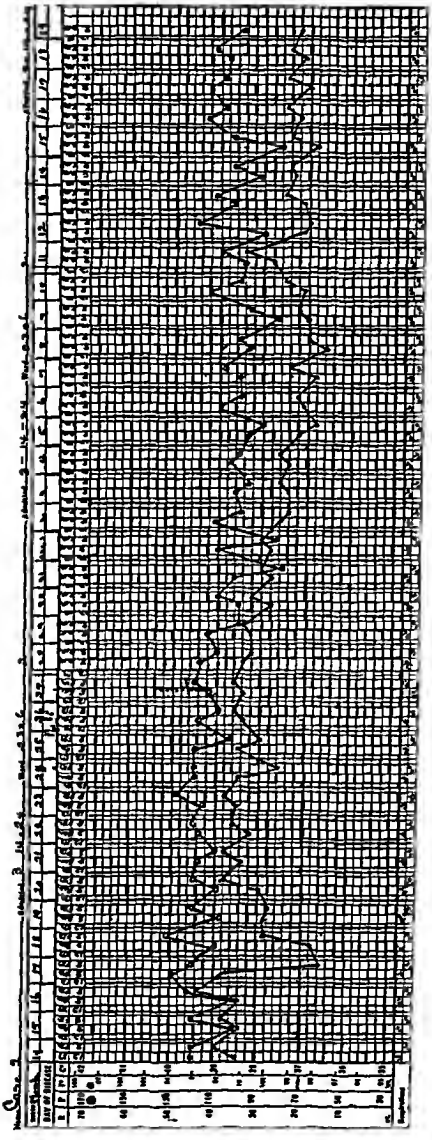

Fig 59

per cent On the tenth postoperative day, leukocytes, *13,000;* polymorphonuclears, 74 per cent On the twelfth postoperative day leukocytes were 12,000 and on the fourteenth postopera-

tive day 8,000 with 74 per cent polymorphonuclears The red cells and hemoglobin were as follows

Eleventh postoperative day, red cells, 3,500,000, hemoglobin, 72 per cent
Thirteenth postoperative day, red cells, 3,650,000, hemoglobin, 75 per cent
Eighteenth postoperative day, red cells, 4,240,000, hemoglobin, 79 per cent

Glycosuria and glycemia were controlled with 90 units of insulin and a diet of 1400 calories Later the insulin dose was reduced to 60 units per day At the end of the first postoperative week the pulmonary condition had improved greatly, but the patient's general condition was worse and was summarized as follows

Drowsiness, from which patient could be aroused Rapid, shallow respirations, over 30 per minute High temperature Contracted pupils, not due to narcosis Many negative blood-cultures and gradually developing anemia

The condition of the stump during the first eight postoperative days was characterized, first, by the lack of infection, second, by the extreme jelly-like flabbiness and loss of tone of the muscles of the stump, and, third, by the total lack of healing or development of granulation tissue Eight days after the operation a profuse discharge from the stump was noted, this was undoubtedly colon bacillus infection The removal of the sutures and the establishment of abundant drainage did not influence the temperature Within three days drainage had practically ceased By the twelfth postoperative day there was definite breaking down of the flaps and some discoloration was noticed, also the beginning of a slough By the seventeenth postoperative day a line of demarcation and definite separation of slough could be noted The first appearance of granulation tissue was noted at this time With the appearance of granulation tissue the temperature began to go down and the general condition of the patient was markedly improved On the twenty-fourth postoperative day there was evidence of a mild cystitis The albumin, which was in such large amounts when the patient entered the hospital, had almost disappeared one month after operation

when patient was discharged Examination of the amputated leg showed beginning endarteritis of the femoral artery, with a clot at bifurcation of popliteal artery into the anterior and posterior tibial arteries This clot included all three arteries of the leg The dissection of the arteries showed very little, and the walls of the smaller arteries of the leg showed no obliterative endarteritis The condition then was one of thromboangiitis

This case showed many of the symptoms of the first one, but was complicated by cardiac failure Still it was quite definitely shown that the congestion and pneumonia was not the cause of the intoxication which developed after amputation The cause of the gangrene was different from the first case, in that here it was due, not to obliteration of the arteries by endarteritic process, but to a thrombosis at the bifurcation of the popliteal arteries Nevertheless the examination of the left leg gave abundant clinical evidence that there was a deficiency in the blood flow through the leg, as shown by the colorless skin and the absence of pulsation in the arteries of the feet

During the time that the patient was most intensely ill, she was transfused (400 c c of blood) Improvement was rather marked following transfusion The stump of the femoral artery was seen to pulsate in the mass of necrotic tissue The femoral artery was apparently quite good at the time of amputation In spite of these evidences of good circulation, the patient exhibited all of the signs of failure to heal and of intoxication, due apparently to products of autolysis

Case III—B White woman, age forty-eight

History—Came to hospital complaining of sore toe No diabetes in family Has been losing weight for eight years Three years ago feet began to be painful, felt numb and cold, and ached a great deal, especially at night Two years ago abscess of great toe of right foot, which healed very slowly Four months before admission noticed excessive thirst Three weeks before admission right foot became worst, throbbed and pained a great deal At this time an ulcer appeared on middle

toe of right foot, which began to drain Sugar was found one and a half weeks before admission to hospital

Examination—Height, 63 inches, weight, 136 pounds Temperature, 100° F , pulse, 95 Skin of face is very thick, dry, and coarse Hair of head is dry and brittle, scanty Pupils are small and irregular Thyroid is very small Chest negative Heart negative, sounds are clear Marked relaxation of abdominal wall, abdomen otherwise negative Knee-jerks very sluggish, ankle-jerks absent Arteries Pulsation of left dorsalis pedis artery absent, the posterior tibial pulsation is present in this foot Pulsation of both of these arteries present in the right foot Marked hypalgesia of both feet The plantar surface of right great toe shows signs of purulent discharge *x*-Ray picture shows osteomyelitis of all segments of the second toe and terminal segments of the great toe

Laboratory—Leukocytes, 12,000, polymorphonuclears, 77 per cent , red blood-cells, 4,800,000, hemoglobin, 90 per cent , Wassermann negative Blood-sugar, 0 214, non-protein nitrogen, 28 mgm per 100 c c blood Urine Large amount of sugar, faint trace of albumin, few hyaline casts Moderate ferric chlorid reaction Electrocardiogram, normal heart

Course in Hospital—Dr Barney Brooks made an incision in the right great toe twenty-four hours after admission and amputated the second toe Wounds left wide open and Dakin tubes inserted Patient was prepared for operation with insulin and glucose Recovery was very satisfactory, temperature and pulse as shown in chart (Fig 60) For two weeks after the operation temperature was slightly elevated and then became definitely septic The plantar surface of right foot was opened wide Two positive Staphylococcus aureus blood-cultures were obtained at this time After the foot had been opened, two negative cultures were obtained, but during the week following the second operation the temperature rose and amputation was thought desirable Before amputation, a further incision was made in plantar surface of right foot, which revealed the fact that all of the small muscles of the foot were necrotic and mushy, there was apparently more necrosis than infection Following

when patient was discharged Examination of the amputated leg showed beginning endarteritis of the femoral artery, with a clot at bifurcation of popliteal artery into the anterior and posterior tibial arteries This clot included all three arteries of the leg The dissection of the arteries showed very little, and the walls of the smaller arteries of the leg showed no obliterative endarteritis The condition then was one of thromboangiitis

This case showed many of the symptoms of the first one, but was complicated by cardiac failure Still it was quite definitely shown that the congestion and pneumonia was not the cause of the intoxication which developed after amputation The cause of the gangrene was different from the first case, in that here it was due, not to obliteration of the arteries by endarteritic process, but to a thrombosis at the bifurcation of the popliteal arteries Nevertheless the examination of the left leg gave abundant clinical evidence that there was a deficiency in the blood flow through the leg, as shown by the colorless skin and the absence of pulsation in the arteries of the feet

During the time that the patient was most intensely ill, she was transfused (400 c c of blood) Improvement was rather marked following transfusion The stump of the femoral artery was seen to pulsate in the mass of necrotic tissue The femoral artery was apparently quite good at the time of amputation In spite of these evidences of good circulation, the patient exhibited all of the signs of failure to heal and of intoxication, due apparently to products of autolysis

Case III —B. White woman, age forty-eight

History —Came to hospital complaining of sore toe No diabetes in family Has been losing weight for eight years Three years ago feet began to be painful, felt numb and cold, and ached a great deal, especially at night Two years ago abscess of great toe of right foot, which healed very slowly Four months before admission noticed excessive thirst Three weeks before admission right foot became worst, throbbed and pained a great deal At this time an ulcer appeared on middle

toe of right foot, which began to drain Sugar was found one and a half weeks before admission to hospital

Examination—Height, 63 inches, weight, 136 pounds Temperature, 100° F , pulse 95 Skin of face is very thick, dry, and coarse Hair of head is dry and brittle, scanty Pupils are small and irregular Thyroid is very small Chest negative Heart negative, sounds are clear Marked relaxation of abdominal wall, abdomen otherwise negative Knee-jerks very sluggish, ankle-jerks absent Arteries Pulsation of left dorsalis pedis artery absent, the posterior tibial pulsation is present in this foot Pulsation of both of these arteries present in the right foot Marked hypalgesia of both feet The plantar surface of right great toe shows signs of purulent discharge *x*-Ray picture shows osteomyelitis of all segments of the second toe and terminal segments of the great toe

Laboratory—Leukocytes, 12,000, polymorphonuclears, 77 per cent , red blood-cells, 4,800,000, hemoglobin, 90 per cent , Wassermann negative Blood-sugar, 0 214, non-protein nitrogen, 28 mgm per 100 c c blood Urine Large amount of sugar, faint trace of albumin, few hyaline casts Moderate ferric chlorid reaction Electrocardiogram, normal heart

Course in Hospital—Dr Barney Brooks made an incision in the right great toe twenty-four hours after admission and amputated the second toe Wounds left wide open and Dakin tubes inserted Patient was prepared for operation with insulin and glucose Recovery was very satisfactory, temperature and pulse as shown in chart (Fig 60) For two weeks after the operation temperature was slightly elevated and then became definitely septic The plantar surface of right foot was opened wide Two positive Staphylococcus aureus blood-cultures were obtained at this time After the foot had been opened, two negative cultures were obtained, but during the week following the second operation the temperature rose and amputation was thought desirable Before amputation, a further incision was made in plantar surface of right foot, which revealed the fact that all of the small muscles of the foot were necrotic and mushy, there was apparently more necrosis than infection Following

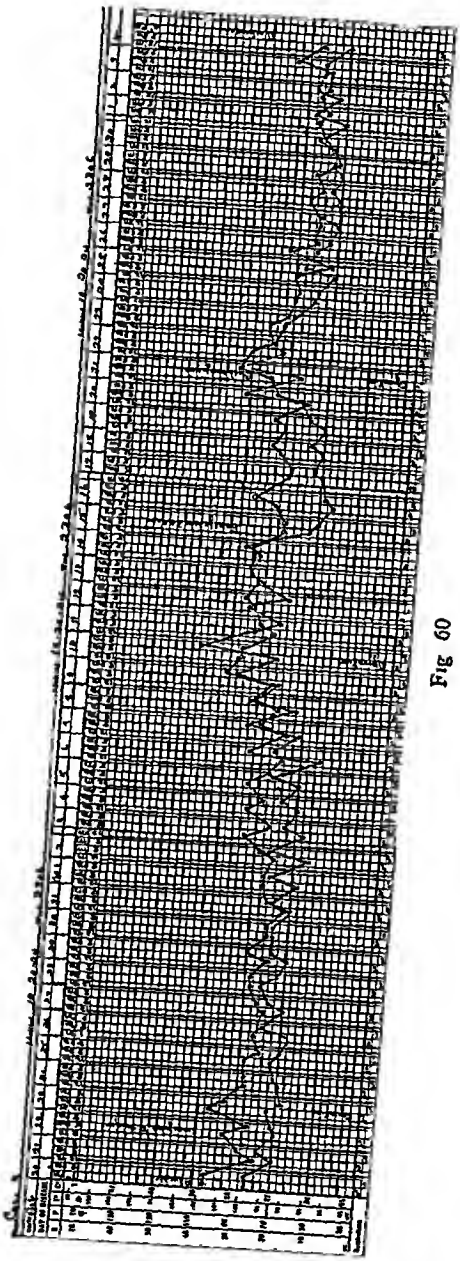

Fig 60

operation patient was transfused 340 c c Healing of the stump was prompt Leukocytes at the time of the positive blood-culture were 12,000, with polymorphonuclears 80 per cent Before amputation the leukocytes were 8000, polymorphonuclears, 87 per cent Red blood-cells, 3,800,000 Patient never showed the shallow, rapid respirations seen in the other cases reported, nor was the pulse-rate abnormally rapid Neither was there evidence of marked drowsiness as seen in the other cases

Diabetic Condition—This was satisfactorily controlled with 40 units of insulin on a diet of from 1400 to 1800 calories Non-protein nitrogen never rose above normal, although the urine usually contained some albumin without casts The phthalein output was 55 per cent in two hours

This case is included in order to show the clinical picture of true septicemia, in contrast with the other 2 cases, where septicemia was not found The prompt healing of the amputation stump and the failure of development of any symptoms seen in the other cases after amputation proves the absence of necrosis and autolysis

Before amputation for diabetic gangrene the clinical picture is usually that of systemic intoxication If amputation is carried out at a level high enough above the infection, it is possible to obtain amputation wounds free, in most instances, from infection We believe that in the above cases the picture seen after amputation is not due to infection of the tissues of the stump

Insulin prolongs life so that it is possible now to study these cases, where before we had insulin the patients usually died The last 2 cases would have died without the help of insulin Insulin makes it possible to give enough carbohydrate in the diet so that even with a high metabolism, acidosis does not occur

The question arises, Is the clinical picture after amputation due to infection in the amputation stump? The leukocytosis, fever, and increasing anemia certainly point to infection, the temperatures as seen in the first 2 cases are not of the septic type In the third case at three different times, we see the

development of a typical septic temperature In this case, where systemic infection was proved to be present, the clinical picture was not the same as that seen in the other 2 There was no drowsiness, the pulse was not so rapid, the leukocystosis was not so great, the respirations were not the shallow rapid type, and the amputation stump healed promptly in a few days

To summarize, then, the picture seen in the first 2 cases At operation neither of these cases bled profusely, the circulation, even in the small arteries and capillaries was very poor, the stump itself always remained very jelly-like and flabby, and there was very little reaction to healing Granulation was never seen in the first case, and in the second case it occurred only at the end of two weeks In the first case necrosis was proved by biopsy after death Microscopic sections of the muscles revealed decided decrease in striation

The systemic group of symptoms were marked drowsiness, almost stupor, continued high, irregular fever, very rapid pulse, and rapid respirations which were particularly shallow in type, unusually high neutrophilic leukocytosis, the absence of any evidence of failure of kidney function, the negative blood-cultures, and, finally, the small contracted pupils

The cause of the intoxication, we are inclined to believe, is due to an autolysis of the tissue in the stump, and this, in turn, is due first, to a definite impairment in circulation, as shown by the lack of oozing of blood at operation and by the finding of arterial disease in the amputated limbs, and, second, to the loss of power to heal in the tissues

The autolysis of muscle *in vitro* has been studied by Bradley,[1] who has shown that muscle tissue differs from other organ tissues in that it resists autolysis to a marked degree At the end of two weeks only 10 per cent of muscle protein undergoing autolysis (*in vitro*) had broken down into amino-acids

If one sections the nerves of the limb *in vivo*, atrophy occurs very rapidly and in two weeks' time 20 per cent of the muscle tissue may have disappeared

[1] Bradley, Jour Biol Chem , 1924, lxi, p 807

It has been shown by Brooks[1] that in a few weeks' time practically all of the muscles of a limb in which the blood-supply has been cut off may atrophy Bradley further showed that if denervated muscles, which have undergone 20 per cent atrophy, be autolyzed *in vitro*, autolysis is more rapid and more tissue is autolyzed than in the case of normal or unatrophied muscles In these cases we have tissues, chronically deprived of blood-supply, apparently undergoing autolysis *in vivo* The ability of the normal organism to absorb denervated muscle tissue (atrophy) or to absorb muscle tissues deprived of blood-supply may be closely related to its ability to heal wounds The power to heal must be the determining factor which ordinarily prevents the occurrence of autolysis

Does the presence of infection in the stump promote autolysis? It can be seen that there is no definite period of incubation in the first 2 cases, but that the symptoms developed immediately after amputation

Carrel has shown that in tissue cultures, which are old and have ceased to grow, the growth may be stimulated by the addition of embryonic and leukocytic tissue He proposes that these tissues produce a substance which he calls trophones Perhaps this is the substance which is absent in the diabetic organism when healing does not take place and when autolysis occurs

Treatment of these cases consisted in circulatory stimulation with digitalis and caffein sodium-benzoate, the latter drug seemed to be of particular value Transfusion is by far the best agent, and improvement was always noted following its use In the second case, it was following transfusion that improvement began

[1] Brooks, Arch Surg, 1922, vol v, p 188

CLINIC OF DR FRANCIS M BARNES, JR

FROM THE DEPARTMENT OF NERVOUS AND MENTAL DISEASES OF THE ST LOUIS UNIVERSITY SCHOOL OF MEDICINE AND THE DEPARTMENT OF NEUROPSYCHIATRY OF ST MARY'S HOSPITAL
SENIOR CLASS CLINIC IN PSYCHIATRY

MENTAL DEFICIENCY OR DEMENTIA

FOR our clinic today there will be presented rather briefly a number of patients showing the two classes of intelligence defects as represented by two groups, first, the mentally defective, and, second, the demented

In these two groups, though an intelligence defect is present, it is of quite different character In the first you have a congenital defect, whereas in the second you have an acquired defect secondary to functional or organic disease of the brain In the first group again you have those cases which illustrate the feature of mind lack, whereas in the second you have those which illustrate the feature of mind loss In other words, in the first group, those with mind lack, including here for our purpose today, the feeble-minded or congenitally defective, we have those individuals in whom intelligence never did reach a normally high level, a condition of amentia In the second group, those with mind loss however the defect is acquired and we are dealing with individuals who had developed what may be designated as a normally high level of intelligence, but as a result of some disease or injury had suffered a loss of this intelligence, a condition of intellectual deterioration, dementia

It will then be the purpose of this clinic to point out to the class that although the term "intelligence defect' is very broad in its scope covering any subnormal intellectual level, it is not necessarily always of the same character or causation

Intelligence, we may say, is the sum total of functioning of all of those activities of mind for convenience customarily considered under the different headings of perception, memory, association, and judgment This being the case, it becomes evident that any impairment of any one of these steps, so necessarily preliminary to the development of intelligence, would show itself by an impairment of the end-result, that is, intelligence itself Intelligence then may be looked upon as the final result of mental activity, the product of the original mental capacity of the individual brain to develop times the environmental opportunities afforded. Intelligence then grows out of a variable combination of stock and environment, the end-result depending invariably in part upon both of these fundamental elements and the proportion in which each may have been present or exercised

You may ask the question, "Why is it of any importance, if a person is of low intellectual level, to know whether this defect was of congenital or acquired origin" A number of important features enter into consideration of this question and its answer In our first group of the mentally deficient, the condition being present at birth, or shortly thereafter, we have to deal with individuals who lack intellectual, and in addition often physical, development, who have not had the capacity to respond to, we will say, a normal environment, who have not developed on a par with others of equal age, who have not, therefore, been able to benefit from knowledge taught in school, who have not the proper perspective as to responsibility, either morally, legally, or otherwise, but who, however, are capable of a certain amount of specialized instruction, and who may become more or less useful if given this proper and necessary supervision over their life and growth and activities There is then, in this first group of aments, the possibility of some betterment and improvement by appropriate training and supervision, and there is always a large possibility, if the condition is early recognized, of preventing these defectives from coming into conflict, either with society or law, because of their defect and their consequent inability to keep from harmful ways In the second group, however, we have an

entirely different situation Here the individual once attained a fairly normal mental level as a result of the combination of stock and environment, but as a result of disease or injury to the brain has lost this once attained level Dementia, as in this group, usually comes on therefore after childhood, in middle or later life, and it is fundamentally important here to remember that this dementia thus acquired is irreparable and irremediable and usually of increasing intensity and depth Betterment and improvement, are, therefore, practically out of the question Intellectual level once lost through dementia is permanent, and dependent upon its degree care in an institution may become necessary

It is understood, of course, that here we are not using the term "dementia" in the generic sense, as has been done in the past, to mean all forms of insanity Nor are we using it in the more specific sense as is illustrated in the term "dementia paralytica," where the word here has become a part of a diagnostic label of a certain diseased condition Another similar example of this usage is found in the term "dementia præcox" "Dementia," as we will use the term, is not in itself a disease, but is one of the symptoms or symptom-complexes of disease As such it may present itself in connection with various types of psychoses or as the result of brain injury by trauma, hemorrhage, or organic brain disease, and the like

The differentiation of these two groups, one from the other, is not a difficult proposition, provided a thorough history, together with a comprehensive investigation of the individual in question, can be obtained When one speaks of mental deficiency and the examination of defectives, there comes to mind in a foremost place the thought of metric measurements Of these scales for intellectual measurement, we have, in the past two decades, been provided with several different types or modifications of original types The first of these is typified by the Binet-Simon point scale for measuring intellectual development Of this, from time to time, there have appeared different modifications, all, however, in their fundamentals essentially similar to the original A type of test somewhat different from the Binet-

Simon and its decendants is the point scale method of Yerkes, Bridges, and Hartwick This has in its favor that it is much shorter in its application and that the scoring method is more just to the individual under examination Another line of modification has arisen from the early recognition on the part of some of the inapplicability of these tests in the study of adults, namely modifications into an adult scale of intelligence rating From all of these also grew the so-called group tests so extensively used during the World War Like all new tests, these, as others, have been extensively misused and maltreated In certain quarters, there has been prevalent the idea that these mental tests could be used as a yard-stick to mathematically measure the intelligence level in any individual under any circumstances So it is that we not infrequently find overenthusiastic investigators applying them to adults suffering, or who have suffered, from various types of mental disease, such as dementia præcox, paresis, paranoia, senile dementia, and so on

In this connection it is advisable to point out that these tests were originally devised, and their purpose remains essentially the same, to investigate the level to which intelligence had developed and not to determine the level to which intelligence once acquired has fallen They were first devised for measuring the degree of growth of intelligence of children and not for the purpose of rating the intelligence of adults They were primarily then devised for the purpose of studying the extent to which mental growth had occurred and not for the purpose of determining the extent of retrogression of mental growth once attained In the development of the mind during childhood, in the growth of intelligence, in other words, there is a rather steady progression upward in rather uniform fashion with no large gaps or jumps in the normal procedure Therefore, with these tests we can very well measure the extent to which this development has taken place However, where there is a dementia as a secondary process as a result of disease in adult life, retrogression of intelligence does not occur in the same uniform, step-wise manner as the growth of intelligence in childhood and, therefore, we find certain portions of mental activity as factors

going to make up the sum total of intelligence are more greatly impaired than others For instance, memory in a given case may suffer very extensively, more so than attention or perception, and as a result of this we get a more broken up and scattered series of loss of intellectual ability which cannot be accurately and clearly measured by any set of tests of this or other similar character

In medicine we look for various clinical manifestations on which to base a diagnosis of syphilis, the Wassermann reaction being only one test capable of clinical application in the study of the case and only one small part of the examination, as a whole, so also in mental medicine these metric mental tests should be connected in multiple with the clinical investigation of the individual, as a whole, as these tests are but one small part of a complete examination and their results should not be accepted alone and by themselves in the estimation of the mental condition of an individual

Intelligence is not the whole and only function of mental activity and by attempting to measure intelligence by these tests one must remember that various other factors of personality are not taken into consideration, or, if they are, only in such insignificant and secondary proportion that their imprint upon the final conclusion is negligible However, it is aside from our purpose to enter upon any extensive dissertation upon the relative merits of mental tests on this occasion and what has been said was only to point out some of their shortcomings and dangers in their misusage We will probably have occasion to mention them in connection with some of the patients which we will now present

First, we will see some examples of the mentally defective or mind-lack group, the aments

Cases I and II—H and L I am bringing these 2 patients before you together, because of certain similarities in their general condition and appearance They are both about the same age, namely, around fifty They represent the lower grade of development, not exactly idiots, but on the lowest margin of the imbecile

Several general characteristics from the physical standpoint it will be well to point out to you You will notice how small the cranium of each is The microcephalic head with the low forehead and rounded dome, the so-called newel-post head Notice how wrinkled, you might almost say, folded, and how freely movable is the scalp of this specimen It almost seems that the cranium developed too little to fill it Note, also, in both the proportionately enormously enlarged and misshapen ears Though they are fifty years of age the ordinary marks of age are not evident in the usual wrinkling and aged facial expression

They have sufficient intelligence to respond to ordinary simple directions, in other words, to understand simple English, and can use a very few words themselves to make their simplest wants known This one, you see, carries with him a small stocking doll, which he nurses and cares for with extreme solicitude Irritability in this chap is a very marked feature, which, as you see we may easily demonstrate by attempting to take the doll from him

Mentally speaking, one is no better than the other, yet each endeavors with childish simplicity and concern to look after his companion More a case of the blind leading the blind than actual service Their mental ages according to the tests, is around about four, possibly a little lower or higher Owing to the large number of years chronologically which each has lived, there is some scattering which made the tests not quite accurate

We know but little of the history of these individuals other than that they have been in the institution for many, many years, in fact, from early childhood The family history is not known It only takes a casual inspection and no more than general knowledge without medical training to recognize these as mentally defective

Case III —F P , age twenty-eight years This young man I am sure strikes you in the first instance because of the very irregularly shaped form of his head It is difficult to describe in words just what type of malformation with which we have here to deal You will notice these bumps in the posterior temporal

region on either side, the flattening of the occipital region, the low forehead and the rather flat crown The best that we can say is that the head is generally misshapen without any regard to particular type

This boy answers to ordinary directions by corresponding movements, but does not speak intelligently because of a speech defect, another evidence of deficient development In addition to this, on the physical side, you will notice, that the left arm is held in the flexed position and on attempting to move it there is some degree of contracture Also, there is evidence of underdevelopment of this member as compared with the corresponding one on the other side If you will notice his gait as he walks across the room you will see that he uses the left leg rather poorly and progresses with some stiffness and spasticity

Here we have, as we learn from the history, a condition which was congenital or, rather, acquired at birth, so near being congenital that they are practically the same, an infantile palsy due to birth injury of the brain From this results the partial left hemiplegic condition In the family history of this patient we learn that the father was alcoholic and that the mother had tuberculosis We not infrequently find such conditions in the antecedents of the feeble-minded

Case IV —This negro boy is seventeen years of age Notice the very large size of the cranium, a macrocephaly, and, in this case, hydrocephalus Also, you saw as he entered the room the evident hemiplegia of the left side

The mental development in this patient proceeded further than in those which we have previously shown you and he did for a time attend school Mental tests show his mental age to be about seven years In other words, he comes in the class of the imbeciles, according to the Binet-Simon classification This classification, you will remember, divides the feeble-minded into three classes those with a mental age of one or two years are classed as idiots, those with mental age of three to seven years are classed as imbeciles, and those with a mental age of eight to twelve years are classed as morons

Another frequent accompaniment of these mentally deficient states is illustrated in this case by the occurrence of epilepsy This boy has been epileptic since the second year of life He is also extremely irritable at times when crossed and will even attack those about him when he becomes sufficiently irritated He represents a condition of feeble-mindedness, mental deficiency of the imbecile grade resulting from organic disease of the brain, which dates back to early infancy

Case V—J K, aged twenty-nine years The mental age in this case as shown by the test is six years Notice on the physical side this rather rounded and pointed head, coarse, black, straight hair, low down on the forehead, the large ears, the thick neck, the short stubby stature, the protuberant abdomen, and the rather peculiar facial characteristics, small eyes with red lids, the very thick protuberant lips and the thick and large tongue All of these physical abnormalities, as you have learned in your other classes, are evidences of cretinism We have, in this case, an illustration of mental deficiency, feeble-mindedness of the imbecile grade, resulting from disturbance of the endocrine gland function, hypothyroidism, or cretinism

This individual had never received any thyroid treatment until quite recently, in other words, until a period in his existence had been passed beyond which little hope for development might be expected It is true there was some general improvement, particularly on the physical side, from the administration of thyroid some months ago It is possible, as we have learned from our other experiences with these cases, that proper treatment, instituted at a sufficiently early age in this patient, might have resulted in considerable betterment of not only the physical but the mental state

Case VI—L B, aged twenty-six years This young woman presents a somewhat different appearance from those previously shown in that there is nothing unusual to attract attention She is not misshapen physically, her general appearance and behavior appears to be that of a normal individual, she answers

questions about herself and her past life, in general, quite satisfactorily

We find in the history that her mother, incident to the delivery of two of her children, was said to be temporarily insane and that the father was rated as peculiar and high strung In school this woman got along until the sixth grade, though she was not considered bright, and was rated much below the average by her teachers

At about the age of thirteen she had some sort of mental trouble and a diagnosis of hysteria was made This was of temporary duration, an episode of a few days in all, probably nothing more than one of those transient psychic explosions to which defectives are subject She has never carried on any steady occupation, has been more or less irresponsible and easy going, taking nothing seriously It has been learned recently that for a number of years past she has been quite promiscuous sexually and heterosexual relations with some members of her own family are reported The Yerker-Bridges point scale measurement shows a mental age of eight years

Here we have then a young woman who did not get along in school, who was not considered bright, and only reached the sixth grade She has remained about home, taking no responsibility, and in all was looked upon as being below the average mentally The family history also is not good and we have evident stock defects There is a want of development of moral responsibility, with a lack of appreciation of her moral derelictions, as shown by her justification of them by saying she could not resist, a high degree of suggestibility showing itself in the ease with which she was lead into this or that dereliction, no steadfastness of purpose, no stick-to-it-iveness In other words, we see here an example of congenital mental defect not marred by any of the usual physical abnormalities, an individual whose intellectual level was not investigated until recent troubles brought her into difficulty with social custom and who, until recently examined passed as an average normal woman and was treated as such

Cases VII, VIII, IX, and X—We have here a family group which is of interest in showing that feeble-mindedness is in many instances, from 65 to 70 per cent of all cases, an inherited stock defect, and, of course, in most cases this factor plus an environment defect

This woman, the mother, is thirty-five years old Her history shows that she comes from a small country town where the family has been largely supported by charity, that she attended school only but a few years of her early life, going part of the year only to the country school, that she did not get along well with her studies, was never considered bright and, in the parlance of the community, was "weak-minded" Though the mental tests are not considered of value in adults, nevertheless they were here applied and showed that she had a mental age of about eleven years

These are the 3 children This one, the older girl, is fourteen years of age and the mental tests show a mental age of nine years In other words, she is in the lower stretches of moronity This second girl, twelve years of age, shows a mental age of seven years The third child, this boy, is nine years of age, and has a mental development of a child of five years

It is learned that the father was an alcoholic, an ordinary laborer, not at all responsible or steady and deserted the family some years ago It is often this sort of family, with the underlying cause of dependency unrecognized, which helps deplete the resources of community funds Such a family should be institutionalized by the state and not made to attempt an existence for itself with the aid of money and subsistence doled out to it by charitably supported welfare organizations

The preceding series of cases represents illustrations of mental deficiency, mind lack, of the feeble-minded class We have selected some of these cases to show those wherein the mental defect is associated with various physical abnormalities known as stigmata of degeneracy You have seen a case where brain disease, such as hydrocephalus, where brain injury such as that sustained at birth, where other diseases in the parents, as well as feeble-mindedness itself, have been the causal factors in the pro-

duction of this congenital defect which shows itself most strikingly in the lowered intellectual level and less so in personality defect and characterologic anomalies with emotional instability, suggestibility, and the like

In other words, feeble-mindedness is a condition which may result from a number of different causes, some of which it has been the endeavor to bring out in illustration in this clinic We have not attempted to show you on this occasion some of the higher types of intellectual defects such as are seen in the group of defective delinquents, constitutionally inferior and psychopathically constituted individuals These latter ones would require much more elaboration in their presentation on this occasion than there is time at our disposal The intelligence defect then, in other words, is to a lesser degree evident than it is in the feeble-minded, where it is the lack of intelligence primarily which is the predominant factor in the situation These cases will serve then to illustrate the group of mind-lack class known as feeble-minded, and in which intelligence has not developed to a normal degree and in which group in this respect we have the opposite of the dement

We will next observe several patients who represent the loss intelligence or dementia secondary to other functional or organic diseases of the brain and among these we will show patients with dementia præcox, paresis, senile dementia, and brain injury. In presenting these cases, as I have previously stated, the clinical records will be given briefly, as time is not sufficient for us to go into them more adequately than to demonstrate that the dementia is present and that it was secondary to some other brain condition, occurring in an individual who had previously shown an average intellectual development

Case XI —Age, twenty-four years This young woman shows by her appearance and manner of dress and behavior the outward expression of some mental disorder You will note that she sits in a rather stupid attitude with head bowed down, having little interest in what is going on about her and at times she smiles in a rather silly fashion without apparent outward causation

If we go back to the history we find that the onset of the present illness was about two years ago, at which time the patient was working as a stenographer, and at this occupation had reached a high degree of capability She at first became somewhat depressed and sad, crying a great deal and had but little to say to members of her family or others She kept on with her work until rather abruptly she became quite disturbed, crying and laughing and dancing about and otherwise excited She continued excited for some six months, remaining noisy, screaming, and inaccessible For the past two months she has been more or less quiet all of the time, with the exception of occasional periods of excitement and disturbance

It is interesting to note in the history that there was an attack of "flu" about a month before the onset of her present illness, inasmuch as the mental break not infrequently follows closely such an infection This woman before her sickness was of rather sociable type, good natured, but inclined to be irritable at times, and to show considerable temper Her general physical condition reveals nothing of abnormal character and a neurologic examination seems to be entirely negative

As we question her here today we find that she answers some questions appropriately, but, as a rule, is very irrelevant and gives very little information whatsoever concerning herself Attention is difficult to gain and cannot be maintained to any one subject She is quite disoriented in all three fields Her spontaneous production, as you will notice, is of rather rambling character and more or less incoherent Owing to her inaccessibility it is quite impossible at this time to determine whether or not delusions or hallucinations are present There is apparent an instability and fluctuation of the emotional state, the patient laughs in an exceedingly silly fashion at times and during the examination, when objecting to certain procedures of the physical investigation, you will remember that she cried and became quite tearful for a short period, and then this as suddenly disappeared to be replaced by a more normal manner, or even by a state of laughter There is no irritability or apparent anxiety The emotional tone appears to be rather superficial and underneath it all possibly there is a certain degree of indifference

In summary we have here a young woman, who, after taking a business course, worked as a stenographer and office assistant up until the time of the beginning of the present illness After two years of this illness the patient as you see her now shows disorientation, lack of insight, impairment of judgment Her present condition then represents a marked change from her previous normal state of business efficiency and she has fundamental evidences of deterioration, intellectual lowering, or dementia, resulting secondarily from dementia præcox

Case XII —L A , aged thirty-three years

The family history as given by this patient at the time of his admission is probably unreliable, but at all events, so far as can be determined, is negative for nervous or mental disease

This patient is unable to tell exactly where in Germany he was born He attended school between the ages of six and nine and claims he got along well During the next three years he worked on a farm with his father, coming to this country at the age of twelve He is unable to give the year of his arrival in America For three years after coming to this country he worked with his brother in a grocery store and then started one for himself, at which he continued successfully for five years Following this he worked as a grocer in different stores, apparently successfully He denies syphilis, used alcohol moderately, and denies previous illnesses In other words, up until this point in his life we are dealing with an individual who apparently was the average normal and in his contacts with the world at large was successful in the measure of his attainments

The first symptoms appeared about six months ago, he showed marked memory and speech defect, anomalous pupillary reactions, delusions of grandeur, and was quite confused at times There was a positive Wassermann reaction with the blood-serum and spinal fluid, the latter showing an increased cell-count of 44

On admission to the hospital it was noted that he had a marked memory defect, impairment of orientation and insight He answered questions promptly Emotionally he seemed happy

and contented, and at times definitely elated and even euphoric No hallucinations could be determined Physical health was good There was a marked speech defect The left pupil was larger than the right, both irregular in outline, both dilated more than the average normal and absolutely no light reaction either directly or consensually and the accommodative reflex was sluggish Knee-jerks were equally exaggerated His response to routine intelligence tests was markedly inadequate

The disease course has continued practically unchanged, with the exception that at times he becomes somewhat irritable and quite inaccessible, so that little idea of his subjective mental condition can be determined This condition, as we have related it from the record, you have seen this morning continues at the present time There has been a progressive deterioration in the mental sphere, a dementia secondary to organic brain disease, paresis

Case XIII—B H, aged eighty years The changes of senility are easily apparent in this old man as he takes his seat before you The hair is thin and gray, the skin is wrinkled and inelastic and senile His general musculature is quite atrophied, veins and arteries standing out prominently Gait and station are good Strength is fair There are no paralyses or weaknesses You will note that there is a tremor of the hands and forearms, irregular in time, coarse in character Other than for these general changes of senility, general physical examination is quite negative as is also the neurologic, there being no evidence of any focal disease of the nervous system

This patient is quite disoriented for time He does not know the year, month, or day of the week He is apparently oriented for place and person Memory for recent events is very much impaired, he does not know how long he has been here nor why he came nor can he tell the name of any of those about him For remote past memory is fairly good, although it also shows some impairment Insight into his condition is almost entirely lacking He does not appreciate that he is sick, says that he feels quite well aside from his eyes, which are getting a great deal

better under treatment Definite delusions or hallucinations are not elicited His grasp of current events is limited Associational abilities much decreased, comprehension being impaired to a marked extent Intellectual impairment is quite marked The patient, as you saw, required aid in dressing after our physical examination, showing considerable confusion in this procedure, putting on some of his clothing in quite twisted manner

If we look now at the history of this case we find that this man has been a farmer and always in good general health up until somewhat over a year ago when he began to fail generally It was then noticed that he was somewhat restless, memory was becoming poor, at times he would be somewhat irritable This condition has gone on progressively and within the past few months he has occasionally shown some tendency toward vague fears of impending danger, imagining without any foundation, in fact, that something was going to happen to him or some of his relatives

We have then in this case a man well in the senile period who shows the usual physical evidences of senility and whose mental state shows a marked deterioration and impairment of intellect, a dementia secondary to senile changes, in other words, senile dementia

Case XIV—R C, aged fifty-one years This woman has always been in good health, according to the record, and worked daily and in an unusually capable manner as a clerk until about a year ago when she was injured by being struck by a street car She was rendered unconscious by the injury, remaining unconscious for ten days As a result of the injury the skull was fractured and immediately an operation was done in the left temporal region Some two or three months following the injury she became subject to attacks of unconsciousness with convulsions and these have occurred at intervals until the present time Following these attacks she will become quite disturbed and excited

Since the injury her mental state has been abnormal She is childish in her behavior and is not allowed to go by herself

outside of the house At times she is very obstinate and irritable and is always quite childish in her reactions As we look at this patient you will see that the general nutritional state is good Note this large depression in the bone in the left temporal region at the site of the operation As the patient walks you will notice she limps on the right side and this we find is paralleled by weakness of the muscles of the right arm and leg and, also, we find that the tendon reflexes on the right side are all much more exaggerated than those on the left and that there is a definite Babinski and Chaddock on the right

While our examination has been going on I am sure that you have noticed that the patient's general appearance and behavior is somewhat childish She answers questions readily, but not fully, and at times she does not appear to grasp the importance of what is said to her You will remember she gave a quite inadequate account of what has happened within the past several months, memory being very definitely impaired Attention is very easily gained, but not well held to any subject Orientation for time is not accurate Her insight into her condition is not clear, she does not realize fully the mental impairment Judgment is much impaired and comparing her present ability with that of her efficiency prior to the injury it is easily seen that there has been a lowering of the intellectual level, a definite intellectual deterioration, dementia, and all of this secondary to organic disease of the brain accompanied with a right partial hemiplegia resulting from head injury

As our hour is now nearly up I will not bring in any more examples of these secondary dementias, inasmuch as the 4 which you have seen illustrate sufficiently for our purpose the occurrence of dementia as a result of other diseases of the brain In each one the record has shown that the decline in intellectual ability has been progressive and that there has, therefore, been an increasing depression of the intellectual level as the months went by After such a period of time with no improvement, but rather a progressive increase in symptoms I am sure that none of you would expect a recovery in these patients

In comparing the general characteristics of each of these two

groups, that is, the feeble-minded and the demented, there are several features of interest which we might point out at this time In the first place, let us consider the behavior reactions in the two groups In the first the difficulty mainly arose early in life because the individual was unable to take care of himself or herself to such an extent that he or she could live in a community without coming into conflict with law or society As might be expected none of the feeble-minded group had ever progressed to any great extent, none of them had ever developed any business ability and none had entered into any self-sustaining occupation They did not have the mental capacity to plan, and their difficulties were mostly of a puerile and childish character There is evident, fundamentally, a lack of judgment in the first group

On the other hand, in the second group of dements, we meet with individuals who had in each instance developed to somewhat above the average intellectual ability and who had been able to carry on their several businesses with more than average acuity and prosperity The behavior in each one of this group was better than that of the average normal individual under similar circumstances of life Incident to the neuropsychiatric disease which developed and progressively more with its course, there became evident a decided change from the former mental state In some the emotional state was greatly disturbed, memory was impaired, associational activity was reduced to a minimum and judgment became decidedly defective In some there was left an ability to plan for the future, but the impaired judgment made the adequate carrying out of such plans a complete failure

In conclusion then we will repeat that the differentiation between these two groups lies primarily in the fact that the intelligence defect in the aments is one inherent in the individual, congenital, or early acquired, and is a uniform lack of development of intellectual capacity, whereas, in the dements, we are dealing with a symptom of disease resulting from disturbance of function either through functional or organic impairment of the brain, thus secondarily leading to a lowering of intellectual ability which is not uniform in that it does not involve equally all types of knowledge or all mental functions in the same degree

CLINIC OF DR LOUIS H HEMPELMANN

WASHINGTON UNIVERSITY MEDICAL SCHOOL

A CASE OF SPLENOMEGALY ASSOCIATED IN ITS LATER STAGES WITH GREAT INCREASE IN BOTH THE WHITE AND RED BLOOD-CELLS

CASES of splenomegaly associated with a great increase in both the white and red cells are very rare and very well worth calling to your attention

The patient, unfortunately, died recently, but a consideration of the case with discussion will, I am sure, prove interesting and instructive

There seems to be a close relationship between the erythrogenetic and leukogenetic functions of the blood-forming organs, as will be shown by a report of the following case which was under more or less constant observation for a period of over three and one-half years

Miss A S, fifty-nine years old, public school-teacher, came under observation on March 3, 1920, because of an acute gastric attack In the course of the routine physical examination, a very much enlarged spleen was discovered The patient informed me that she had been aware that her spleen was enlarged for at least five years, at which time an osteopath had told her of its presence She had had no discomfort except a dragging pain in the upper left abdomen whenever she was on her feet much Had been losing slightly in weight lately and complained some of anorexia and a tendency toward diarrhea

Family History—Both parents supposed to have died of paralysis No history of tuberculosis or malignancy in the family

Previous History —Had an attack of acute articular rheumatism nine years ago which confined her to her home (most of the time in bed) for three months Has always been subject to migraine Formerly had frequent spells of bronchitis (asthma?), but has not had so many attacks recently Uneventful menopause at forty-eight Has never vomited blood, but has had occasional slight bleeding from hemorrhoids No history of chills and fever

Physical examination showed a well-nourished woman, about 5 feet, 4 inches tall and weighing 154 pounds The skin and visible mucous membranes were normal The teeth were in poor condition (pyorrhea), tonsils negative, thyroid normal Heart and lungs normal The spleen was very much enlarged, measuring 26 cm in the long diameter and 24 cm in the transverse The surface was smooth and the notch was easily palpable The liver was not enlarged and the other abdominal viscera were normal

Urinalysis —1 012, trace of albumin, no sugar, a few leukocytes on microscopic examination

Blood-pressure —136/90

Blood Examination —Red blood-cells, 5,184,000, white blood-cells 10,600, hemoglobin, 75 per cent , Dare, the stained specimen showed some polychromatophilia, a few normoblasts, an occasionl megaloblast (6 normoblasts and 3 megaloblasts in 250 white cells counted), differential[1]

	Per cent
Polymorphonuclears	64
Large mononuclears	21
Small mononuclears	3
Large lymphocytes	1
Small lymphocytes	5
Eosinophils	½
Transitionals	5

A provisional diagnosis of early Banti's disease was made and the patient was watched for the next three months She continued to teach throughout this time, although she frequently

[1] Many of the leukocytes were atypical and difficult to classify and would probably have been listed differently by another hematologist

complained of weakness and fatigue and spoke of the dragging pain in the upper left quadrant and of some pain in the left leg The spleen remained stationary and she lost slightly in weight, viz , 3 pounds in three months

On June 16, 1920, the blood examination showed red blood-cells, 5,168,000, white blood-cells, 12,000, hemoblogin, 80 per cent , Dare, differential[1]

	Per cent.
Polymorphonuclears	73
Large mononuclears	16
Small mononuclears	2
Large lymphocytes	4
Small lymphocytes	2
Eosinophils	2
Transitionals	1

Normoblasts, 6 in 300 white blood-cells counted

The fasting blood-sugar was 0 113 mg per 100 c.c of blood and the N P N was 20

At this time she was seen by Dr George Dock in consultation Dr Dock concurred in the opinion of probable Banti's disease and both he and I advised splenectomy, which was performed on June 26, 1920 The spleen measured 28 by 14 cm and weighed 2215 gm (4 lbs , 14 oz) Dr R Buhman examined the specimen microscopically and reported

"Sections from spleen Miss S , show the capsule and the connective-tissue trabeculæ very markedly thickened Many of the malpighian bodies are partly replaced with connective tissue Several areas show a number of multinucleated giant-cells "

The wound healed per primam, but she developed a pyelitis which made her convalescence rather tedious Two months after the operation the blood examination showed red blood-cells, 4,080,000, white blood-cells, 26,600, hemoglobin, 60 per cent Differential[2]

[1] Many of the leukocytes were atypical and difficult to classify and would probably have been listed differently by another hematologist

[2] Ibid

	Per cent
Polymorphonuclears	60
Large mononuclears	1½
Small mononuclears	1½
Large lymphocytes	3
Small lymphocytes	28
Eosinophils	3
Transitionals	3

Normoblasts, 3 in 314 white blood-cells counted

She improved slowly after this time, although she had several flare-ups of her pyelitis In March, 1921 she had a moderate edema of the feet and legs and was slightly dyspneic on exertion There was a systolic murmur at the apex and the second pulmonary was accentuated The heart, too, was enlarged toward the left and the liver was enlarged At this time the white blood-cells numbered 48,600 and the stained specimen showed many normoblasts, at times, 2 to a field, and a few megaloblasts She was given digitalis and improved, although the liver remained enlarged and the heart murmur persisted At about this time she had all her teeth pulled because of the pyorrhea She improved slowly for the next six months, although she had occasional spells of indigestion and also peculiar neuralgic pains in the legs

In October, 1921, sixteen months after operation, the white count was 61,600 and the stained specimen showed many nucleated reds The heart was in fairly good shape and her wind was good, but the liver was much enlarged She seemed to feel fairly well for the next four months, was able to teach, but had occasional vomiting spells and a few asthmatic paroxysms The whites gradually increased so that by the middle of February (twenty months after operation) they had reached 131,200 A differential[1] count made January 14, 1922 showed

[1] Many of the leukocytes were atypical and difficult to classify and would probably have been listed differently by another hematologist

	Per cent
Polymorphonuclears	66
Large mononuclears	12
Small mononuclears	5
Large lymphocytes	3
Small lymphocytes	5
Eosinophils	1
Transitionals	6
Basophils	2

Nucleated reds, 31 in 200 cells counted

x-Ray treatment was suggested at this time, but was declined for lack of time and because of the expense involved Benzole was begun in February, 1922 in doses of 10 gtt three times a day, and in three months the white count had gone down to 63,200 She felt better, in general, but soon the white count rose slowly, reaching 100,000 in the next three months, *i e*, in June, 1922 (two years after operation)

During the next six months she did not do so well She was quite dyspneic at times and complained of a feeling of weakness Slight edema of the ankles was present off and on She was nervous and slept poorly The white count varied from 78,000 to 126,000 She took benzole and digitalis most of the time and arsenic in the form of asiatic capsules, too, off and on From November 25, 1922 to December 30, 1922 the count fell rapidly to 46,600 and there was a decided improvement in her general condition Throughout the next six months she did fairly well, was able to teach, but had several spells of "neuritis" and also an attack of grippe The white count varied from 46,600 in December, 1922 to 79,800 in June, 1923

During the next four months she did poorly, she felt weak, had a good deal of "neuritis" in her legs, and quite a bit of headache The heart was doing fairly well The blood-pressure was 196/110, but the liver was enormously enlarged, the lower border going down to the umbilicus It measured 8 cm in the vertical diameter in parasternal line and $7\frac{1}{2}$ cm in the median line I had noted an increasing cyanosis which began about September, 1923 and was rather too pronounced to be accounted for by the heart condition A blood-count on October 6, 1923 revealed red blood-

cells, 9,926,000, white blood-cells, 86,400, hemoglobin, 105 per cent Another count made two weeks later showed red blood-cells, 9,800,000, white blood-cells, 91,400, hemoglobin, 98 per cent Recently she had had several attacks of vertigo, during one of which she fell on the street The last blood examination was made on November 24, 1923, at which time the red blood-cells were 7,136,000, white blood-cells, 102,000, hemoglobin, 102 per cent The pulse was 84 and she complained of some vertigo and a full feeling in the head She died in the schoolroom four days after this examination (three and one-half years after operation) apparently of some cerebral lesion She was found sitting in a chair unconscious during her lunch hour and died one hour later There was no postmortem

Discussion.—A woman fifty-nine years of age who had had a very much enlarged spleen for years, with practically normal blood-count, is splenectomized Soon after operation the white count begins to go up, reaching 131,000 twenty months after operation In the meantime she has developed a mitral insufficiency with symptoms of incompetency off and on and a liver almost too much enlarged to be accounted for by the stasis The white count remains elevated in spite of benzole and somewhat over three years after operation a cyanosis is noted At this time, the red cells are found to be near 10,000,000 and the hemoglobin 105 per cent Death from some cerebral lesion two months later

What is the explanation of this series of events?

It may perhaps be well to confess at once that the course of the disease after the splenectomy did not verify our diagnosis of Banti's disease I do not believe, however, that the splenectomy affected the course of the disease very much in any way Splenectomy in normal individuals is followed by a temporary leukocytosis and later by an anemia which reaches its height five or six weeks after operation, after which the blood gradually returns to the normal The high percentage of polymorphonuclears raises the question of some possible infection, but the entire absence of fever and the long duration of the disease would speak against this assumption

The presence of the mitral insufficiency and enlarged liver might make one think that possibly the high red count was dependent on the heart condition, but the presence of the nucleated reds and enormous size of the liver would speak against this diagnosis Then, too, one never sees red counts of 10,000,000 in chronic heart disease It seems probable to me that this case belongs to a small group of cases in which the symptoms of an erythremia and leukemia coexist or perhaps merge into one another

It is, of course, conceivable that our patient was in the aleukemic phase of a splenomyelogenous leukemia when first seen and that the later increase in white cells was only the natural course of events in a leukemia The increase in the red cells, while very unusual in leukemia, has, nevertheless, occurred as in the case of Winter's which will be abstracted shortly

Pendergrass and Pancoast, of Philadelphia, wrote an article which appeared in the June, 1922 number of the American Journal of Medical Sciences on the "close relationship of the erythrogenetic and leukogenetic functions of the bone-marrow in disease" and report a case of a man sixty years of age who had had an enlarged spleen for years when he first came under observation in June, 1916 The blood examination at this time showed red blood-cells 5,200,000, white blood-cells, 7,200, hemoglobin, 90 per cent In September and October of 1917 he showed a tendency to hemorrhage (bleeding from teeth and after striking thigh) and in December, 1917, the blood examination showed red blood-cells, 5,810,000, white blood-cells 45,200, hemoglobin, 78 per cent He was given x-ray treatments At one time the red cells reached 9,000,000, but when last seen, April, 1922, the count was red blood-cells, 5,160 000, white blood-cells, 11,800, and hemoglobin, 95 per cent. The authors believe that "if there is a midgroup between erythremia and myelogenous leukemia or if the two are ever combined," the case they report should come under this head

Minot and Buckman, in an article on erythremia published in the October, 1923 number of the American Journal of Medical Sciences, take very much the same view as shown by their conclusions, viz ,

"The increased activity of the marrow in erythremia is reflected in the peripheral blood by increases of all three formed elements originating from it—erythrocytes, leukocytes, and platelets It is evidenced likewise by the appearance of abnormal and immature forms of all three elements, which may occur in greatly augmented numbers The blood-picture may then resemble that of myelogenous leukemia

"Three cases are recorded that, after having polycythemia for many years, developed anemia, coincident with a further increase in the size of the spleen and a leukemic blood-picture One of these cases was examined postmortem The spleen, liver, and bone-marrow showed a hyperplastic blood formation very similar to that seen in myelogenous leukemia

"Myelogenous leukemia and erythremia appear intimately related, and both may be of a neoplastic nature There occur cases of erythremia and leukemia that illustrate multiple varieties of varying degrees of primary pathologic activity of the myeloid tissue, which usually conforms to a definite type"

They even advance the hypothesis that both may be of neoplastic nature and report 3 cases of polycythemia which developed a leukemic blood-picture, with anemia in the later stages of the disease

That the two diseases are closely related is shown by the case of Hedinius A woman sixty-five years of age, with enlarged spleen, had a red count of 6,500,000, white, of 4,200, and hemoglobin, 109 Two years later the red went up to 11,540,000 and still at autopsy the case was found to be a typical myelogenous leukemia

Rosin's case is also interesting A woman fifty-two years of age, with a red count of 10,000,000, was seen by Friedrich Mueller, who made a diagnosis of erythremia Five years later she was under Rosin's observation with a red count of 3,500,000, white blood-cells, 48,000 to 52,000, and a differential count suggestive of, but not typical of, leukemia

Winter's case A man forty-six years of age had an enlarged spleen for six years He was studied by Krause, of Jena, in 1904, who found red blood-cells, 4,800,000, white blood-cells,

22,600, hemoglobin 110 per cent, 65 per cent polymorphonuclears and 30 per cent myelocytes, and diagnosed myelogenous leukemia Three years later red blood-cells numbered 8,292,000, white blood-cells, 23,200, when a diagnosis of erythremia was made The polymorphonuclear, and mononuclears were increased and the lymphocytes decreased

In conclusion, I would like to call attention to the fact illustrated by this case and those cited from the literature, that there is a close relationship between the erythrogenetic and leukogenetic function of the bone-marrow and that cases occur which at times show the typical picture of a myelogenous leukemia and later terminate with the picture of a polycythemia and vice versa

CLINIC OF DR J CURTIS LYTER

St Anthony's Hospital

METASTATIC CARCINOMA OF THE BONE-MARROW AND SPLEEN

The first case for study and discussion is that of a married woman, thirty-two years of age, who was perfectly well from childhood until in July, 1923, when she noticed a tumor in the right breast This tumor was immediately removed by a surgeon and the pathologic report was carcinoma Recovery from the operation ensued and no further treatment was administered until in the latter part of August of the same year, when she was sent to an x-ray laboratory for deep x-ray therapy During the following two months she received fifteen x-ray treatments, each of which was followed by nausea, vomiting, and general prostration These treatments were discontinued after two months By this time she complained of severe general weakness, loss of appetite, some edema of the feet, constipation, and a marked pain from the left hip to the knee This pain was dull, aching, and continuous It was not increased or alleviated by either rest or movement of the left leg, thigh, or pelvis These symptoms progressed until she entered St Anthony's Hospital on February 22, 1924 By this time the general weakness had progressed to general prostration There was a complete loss of appetite, marked edema of the limbs and feet, profound general anemia, and severe, continuous, dull pain in the left hip and thigh

Physical examination at this time informed one of the extreme paleness of the conjunctivæ, mucous membranes, skin, and nails, marked general emaciation, dryness and looseness of the skin, general muscular wasting, dryness of the hair, and moderate edema of the lower extremities The heart measured 10 cm

in its transverse diameter, there was a soft, localized systolic murmur at the apex, and an accentuation of the aortic second sound The blood-pressure was systolic, 150, diastolic, 80 The spleen and liver were both palpable during deep inspiration One was unable to elicit any abnormal findings upon examination of the nervous system, lungs, other abdominal organs, the pelvic organs, or the bones and joints During the following month she remained in the hospital and upon eight separate examinations of the urine the positive results were as follows Sp gr , 1 005 to 1 010, reaction acid, albumin, 2+, at times a moderate number of hyaline and granular casts and always a moderate number of epithelial cells The blood examinations gave the following results The blood was anticomplementary to the Wassermann test, hemoglobin, 44 per cent , erythrocytes, 1,790,000, leukocytes, 6300, of which there were small lymphocytes, 12 per cent , large mononulcears, 23 per cent , endothelial cells, 3 per cent , polymorphonuclears, 61 per cent , and eosinophils, 1 per cent There were numerous microcytes, megalocytes, and poikilocytes, with a moderate number of megaloblasts and microblasts The polymorphonuclear cells were small and dense, the volume index increased, and the color index was 1 2

With the moderate cardiac hypertrophy, the moderate elevation of the systolic blood-pressure, and the urinary findings, one could feel certain that there was present a moderate chronic nephritis, but an acceptance of this as an explanation of the anemia, general weakness, emaciation, edema, and loss of weight was impossible The clinical picture together with the blood findings were so very typical of primary pernicious anemia that one would be inclined to render this diagnosis were it not for the positive evidence of carcinoma of the right breast a few months previously It is probable that fewer mistakes will be made in analyzing those rather obscure clinical pictures which so frequently follow the early surgical treatment of breast carcinoma if the picture is viewed as the result of a recurrence of the carcinoma in the form of metastasis Very frequently are internists confronted with such vague clinical pictures and almost in each instance there ultimately emerges a carcinoma At times it is

so very unusually located as to render an early recognition impossible Following the early surgical treatment of mammary carcinoma the patient may present a symptom-complex similar to our patient, leading one into a diagnosis of primary pernicious anemia At other times the symptoms are those of chronic arthritis of one or many joints, while frequently the symptoms may be those of an early and mild neuritis In all such instances sooner or later there is discovered a carcinoma in the osseous or nervous systems

In our present case there was another factor to be studied carefully That was the results of the deep x-ray therapy upon the bone-marrow After observing the production of a rather severe type of anemia in a number of patients by deep x-ray therapy one may wonder if in a case similar to the present one the anemia is not after all the result of a superdestruction of the red cells by the reticulo-endothelial system In this instance the x-ray would act to stimulate a normal function of the reticulo-endothelial system with the result that eventually the function became abnormal and the superdestruction resulted in the severe anemia This was primarily our conception of this case since numerous careful studies of the patient failed to reveal any tangible evidence of carcinoma anywhere

Under this conception the patient was given 500 c c of citrated blood by transfusion each week for six weeks At no time did the red cell-count exceed 2,800,000 per cubic millimeter and the color-index remained always above 1 This seemed to be, in the light of our previous experience with blood transfusion in x-ray anemia, profound evidence against an anemia produced by x-ray therapy The patient developed a pulmonary edema on March 20, 1924 and died five days later

An autopsy was obtained and the following is the report of the pathologist

Heart, hypertrophy, left lung, histologic, right lung, pulmonary edema (marked), liver, fatty degeneration, kidneys, interstitial nephritis, spleen, carcinoma, ribs, carcinoma of the bone-marrow

The important pathology in the case, of course, is the metas-

tatic carcinoma of the bone-marrow and spleen In so far as I am able to learn, no such case has been previously reported It is very probable that the presence of the carcinoma in the bone-marrow so affected the reticulo-endothelial system that it produced an anemia very similar in all phases to a primary pernicious anemia

MASSIVE PERICARDIAL ADHESIONS FOLLOWING ACUTE RHEUMATIC FEVER

THE next case to be studied is that of a boy twelve years of age, who five years ago had measles, followed immediately by an acute rheumatic fever, most of the joints of the extremities being involved in the syndrome Associated with the acute rheumatic fever and continuing for two years after its subsidence there was some cardiac disturbance associated with dyspnea, cough, cyanosis, and edema of the feet Following the recovery from this syndrome the boy was well until four months ago, when a similar acute joint syndrome made its appearance Associated with this was tachycardia, precordial pain, cough, dyspnea, and edema of the feet This syndrome continued until the patient entered St Anthony's Hospital on April 1, 1924 At that time there were no indications of any joint pathology, but there was observable dyspnea and orthopnea, cough with frothy, pinkish sputum, and marked edema of the feet and limbs to the hips There was no elevation of temperature and the patient's general condition was very unfavorable

Physical examination at this time established the following positive findings

1 *Head and Neck* Enlarged and adherent tonsils Markedly palpable posterior cervical lymph-glands

2 *Lungs* Numerous, coarse, inspiratory crepitant râles over each lung posteriorly from the scapular spine to the lower margin Respiratory rate 34, respiration being very difficult, especially the inspiratory phase

3 *Heart* The apex impulse was neither visible nor palpable There was a moderate systolic retraction of the epigastrium and the third fourth, and fifth left interspaces from the sternum to the midclavicular line There was no definite retraction of the costal cartilages There was a marked systolic thrill over the entire precordium The left border of the heart was 10 cm

and the right border 3 cm from the midsternal line The transverse diameter of the chest was 20 5 cm The poststernal dulness at the second interspace measured 5 cm There was no change in the area of cardiac dulness to correspond with the change in the position of the patient The area of absolute cardiac dulness was obliterated during deep inspiration There was a moderate systolic retraction of the ninth, tenth, and eleventh interspaces on the left, noted while the patient was in the sitting posture Upon auscultation there was a loud, systolic murmur heard over the entire precordium and into the left axilla, with a short, localized, apical diastolic murmur

4 *Abdomen*· The lower margin of the liver was palpable 7 cm below the costal arch at the right midclavicular line There was a slight amount of free fluid in the abdomen

5 *General*· There was observable a rather marked degree of general anemia and emaciation The patient was in marked respiratory distress There was marked edema of the limbs and feet, slight cyanosis of the nails Blood-pressure Systolic, 106; diastolic, 60

6 *Laboratory*—Blood Culture negative, hemoglobin, 50 per cent , erythrocytes, 2,900,000, leukocytes, 8600, the differential picture revealed nothing abnormal Urine Three repeated urine examinations revealed nothing abnormal

A diagnosis of massive adhesive pericarditis subsequent to acute polyarthritis was made The patient died three days later and the pathologist reported the following autopsy findings

1 *Lungs*· Acute congestion

2 *Liver*· Acute congestion with acute hepatitis

3 *Kidneys*· Histologic

4 *Spleen* Acute congestion

5 *Heart* Massive pericardial adhesions with no involvement of the pleura or mediastinum Marked cardiac hypertrophy and dilatation

6 *Valves*· Normal

7 *Endocardium* Normal

Since the massive adherent pericarditis in this case is so closely associated with two very definite attacks of acute rheu-

matic fever, one is at once impressed with the probability of a single etiology for the two diseases Massive adherent pericarditis is not an infrequent disease, Leudet having discovered it, total or partial, in 8 per cent of his autopsies It probably follows pericarditis with effusion more frequently than is generally presumed at present It is probably a very frequent result of acute plastic pericarditis Viewed from this aspect its etiology would necessarily be the same as that of acute pericarditis Acute rheumatic fever, tuberculosis, pneumonia, erysipelas, scarlet fever, and the other infectious diseases are very frequently complicated by pericarditis more or less pronounced In young patients the condition is very frequent following acute rheumatic fever, in fact, it is probably seldom absent in the refractory or recurring types of this infection In "the large rheumatic heart" of Duroziez massive pericardial adhesions are constant Tuberculosis has been practically proved to be the cause of the adhesions in about 30 per cent of the cases by Leudet, Tissier, and Letulle

From the clinical point of view there are two types of massive pericardial adhesions First, there is the type in which the adhesions are confined to the pericardial cavity, that is to say, adhesions between the visceral and parietal layers of the pericardium To this type one formerly gave the name of pericardiopericardial adhesions in contradistinction to the second type, wherein the adhesions encompass not only the pericardium in its completeness but the mediastinal tissues, the lungs, and the pleuræ as well This is the type so persistently described as adhesive mediastinopericarditis These types are distinct pathologically and clinically, but not etiologically There is present always a certain hypertrophy and dilatation of the heart muscle and at times certain endocardial changes, notably valvular defects

The diagnosis of massive pericardial adhesions is probably not so difficult as depicted, if one will only keep the condition in mind when studying diseased hearts Like many other heart diseases it may exist for a longer or shorter time without symptoms, because the myocardium is able to perform its task When functional symptoms do appear they are not distinctive

There are those related to myocardial inefficiency and most frequently depend upon altered pulmonary, hepatic, gastro-intestinal, or peripheral circulation Thus one encounters cough, dyspnea of the various types, swollen, tender liver, various digestive disorders, and edema of the feet and ankles when the myocardium becomes inefficient These are not, however, distinctive in any specific cardiac disease, consequently we must turn to the physical signs for a minute and correct diagnosis It probably serves us better to consider the physical signs under very definite headings

1 *Inspection*—Bulging of the precordium indicates only cardiac hypertrophy in young subjects before ossification of the costal cartilages Permanent precordial retraction, as described by Bouillaud, is of some value if unexplained by rachitic lesions, pleural adhesions, etc Retraction of the precordial interspaces is not distinctive and it may be present in any case of cardiac hypertrophy in subjects with thin thoracic walls It results from a sudden systolic vacuum created around the heart Systolic retractions of the interspaces, costal cartilages, and epigastrium are more valuable and usually indicate adhesions not only between the two layers of the pericardium, but between the pericardium and the parietal, precordial pleura Broadbent's phenomenon, or a systolic retraction of the ninth, tenth, and eleventh interspaces at the postaxillary line is a most valuable one and is due to adhesions between the visceral pericardium and the diaphragm One must consider this as one of the most valuable of all physical signs and, although it may be observed in certain other instances, the rarity of this is such as to impair its value very little as evidence of pericardial adhesions

2 *Palpation*—Personally, the diastolic shock described so minutely by Potain has been of very little value, since it has been observed in so many other conditions and since it is so frequently absent in massive pericardial adhesions The absence of any well-defined, localized apex impulse in a subject with definite cardiac hypertrophy should suggest always to the examiner the possibility of pericardial adhesions Especially is this true when the patient is examined in the left lateral position

The pulsus paradoxus as described by Gnesinger in 1854 and by Kussmaul in 1873 is of value provided no other condition as large pleural effusion or laryngeal stenosis is present

Swelling of the jugulars during inspiration is a valuable but rare sign

3 *Percussion*.—An increase of the area of cardiac dulness is indicative only of the degree of cardiac hypertrophy and dilatation and is devoid of any specific significance with regard to the pericardial adhesions The lack of normal relationship between the area of absolute and relative cardiac dulness is of some importance when there is relatively a greater increase in the area of absolute dulness This is considered as due to adhesions between the pericardium and the parietal pleura Arising from the same cause is the phenomenon of Cejka This is the invariability of the absolute cardiac dulness during respiration

Finally, one must search for the immobility of the area of cardiac dulness and the apex when the patient is placed in first one position and then the other The fixation of the heart in one position is almost conclusive evidence of pericardial adhesions Although very difficult to demonstrate at times, this sign is probably the most valuable It is almost certain to be present whenever the adhesions are sufficiently extensive to produce clinical symptoms

4 *Auscultation*.—There are many auscultatory phenomena which may be present in massive pericardial adhesions Weakening of the heart sounds, friction, rubs, reduplication of the second sound, and the various murmurs may be present These phenomena are without any diagnostic value and for the greater part depend for their presence upon some associated pathology and not upon the pericardial adhesions In general, one may feel certain that auscultation is valueless in the diagnosis of this condition

5 *Radiography*.—Under the fluoroscope one is at times able to note an absence of the lateral displacement of the apex and an absence of the normal descension and narrowing of the cardiac shadow during deep inspiration Obliteration of the cardiophrenic angle and a relative decrease of the amplitude of the

respiratory diaphragmatic movements are fluoroscopic signs of importance In a study of the *x*-ray plates one may observe an irregularity of the cardiac borders when the adhesions are very pronounced

These, I believe, are the most prominent phenomena upon which one must rely for a diagnosis of this rather frequent and interesting condition

THE third case is quite unusual A young lady sixteen years of age gives a history of a cough, expectoration of a mucopurulent sputum, and fever and chills beginning on July 26, 1924 Two days later there was noticed a rather marked laryngeal soreness Following the development of this soreness she became quite hoarse On August 8th she experienced a severe, sudden, inspiratory pain in the right axilla This continued for five or six days and gradually abated At this time there was some dyspnea upon exertion, such as turning in bed The fever, cough, expectoration, hoarseness, dyspnea, and prostration continued until she came to St Anthony's Hospital on August 12th From that date our personal observation ensued

Upon entrance the temperature was 101° F , pulse 112 per minute, and respiration 32 She gave no other symptoms than those described above

Physical examination at this time confirmed the following positive findings

1 *Chest* —Palpation confirmed the loss or resiliency and tactile fremitus of the right chest below the fourth rib Over the same area there was a flat note upon percussion and the absence of the respiratory murmurs, and the spoken and whispered voice sounds Above the fourth rib the percussion note was skodaic. The respiratory murmurs were somewhat decreased and the spoken and whispered voice sounds moderate The left lung revealed nothing other than compensatory breathing

The heart was displaced to the left so that the left border was 2 cm beyond the left midclavicular line Other than this there were no abnormal cardiac findings

The remainder of a very carefully conducted physical examination, both of the chest and the other systems, was negative

2 *Blood* —Hemoglobin, 58 per cent , erythrocytes, 3,360,000, leukocytes, 17,300, of which 82 per cent where polymorphonu-

clears, 10 per cent large lymphocytes, and 8 per cent small lymphocytes A stained smear revealed the absence of malarial plasmodia and abnormal red and white cells The Wassermann reaction, Widal reaction, and blood-culture were negative

3 *Sputum*—The sputum was sanguinopurulent and contained numerous diphtheria bacilli This was demonstrated both by direct differential stain and by growing them upon Loffler's serum

4 *Urine*—The urine upon several examinations revealed no abnormal findings

At this time a diagnosis of laryngotracheal diphtheria was made as a primary diagnosis and a right pleural empyema as a secondary diagnosis

Aspiration of the right pleural cavity yielded a greenish-white, rather thick pus which upon examination by guinea-pig inoculation, growth upon Loffler's serum, and by a direct differential stain was found to contain myriads of diphtheria bacilli

The patient was given 20,000 units of diphtheria antitoxin and forty-eight hours later a thoracotomy was performed The thoracotomy relieved about 1500 c c of pus from the right chest

Following the operation she rapidly recovered and is today well

In looking over the literature, both English and French, I am unable to find reference to any case of pleural empyema secondary to laryngeal or tracheal diphtheria, in fact, it is not discussed as a complication of any type of diphtheria We have in this case, however, apparently an undisputed case of empyema caused by the diphtheria bacilli It is altogether probable that the patient had a secondary bronchopneumonia—at least, in the first instance—produced by the diphtheria bacilli and arising from this bronchopneumonia was the empyema The case is reported because of its extreme interest and rarity

CLINIC OF DR WALTER BAUMGARTEN

ST LUKE'S HOSPITAL

CERTAIN CLINICAL RESULTS WITH DUODENAL LAVAGE

LYON'S extensive and detailed study of the method of duodenal lavage, his application of Meltzer's principle of "contrary innervation" and the results as applied particularly to the diagnosis of gall-bladder conditions and the recognition of types of bile secretion, has provoked wide comment and not a little criticism It is not my purpose to enter upon a discussion of his findings, and the conclusions based upon them Whatever attitude may be assumed toward his work, his publications have served to attract attention to the method, and have popularized its application That much of the application is uncritical, does not detract from its occasional practical usefulness especially in a therapeutic way

Those who have had occasion to use the method in a variety of biliary duct and liver conditions will have stumbled upon therapeutic results, both unexpected and surprising It is two of these conditions which I wish to present

1 The clinical picture of the first is found in patients who complain of what the lay mind has called "biliousness," and which has never conveyed any clear conception to me However, a certain group is characterized by sallowness of prolonged standing, no true jaundice, occasional and sometimes chronic constipation, more or less lassitude, disinclination to mental effort, frequently drowsiness, and periodic attacks of severe headache with an increase with sallowness, culminating in nausea and vomiting of several days' duration, followed by an apparent,

improvement of all symptoms This improvement, however, proves to be only temporary, and the cycle is resumed, to reach a climax at the end of a period extending over weeks or months

This is the group which has been subjected to the traditional routine of calomel and salts, and recently more rationally to the anticonstipation diet For a few individuals this treatment, especially Epsom salts and occasionally an effective anticonstipation diet, has sufficed fairly well Certain others continue to be the victims of the cycle for an indefinite time In these last an effort at biliary drainage has frequently forestalled attacks when given toward the end of the cycle Under repeated drainage the sallowness disappears, the headaches and the subsequent vomiting do not recur With proper attention to a concomitant constipation, and biliary drainage at progressively longer intervals, these patients make an eventful recovery

The clinical findings in this group are usually negative in general, with a normal blood-pressure, normal urinary findings, a moderate secondary anemia The abdominal findings may suggest a chronic appendix, a ptosis, and sometimes indirect evidence of cholecystitis No liver function test, and no cholecystogram has been performed on any case Gastric analyses showed a normal or diminished acidity (both total and free hydrochloric acid) A few analyses of the fasting contents preceding duodenal lavage showed a high initial acidity, but the great majority a low acidity, some of them a deficit The lavage itself yields bile in which a darker second portion can be identified much as Lyon has described It is frequently darker than is normally obtained, but beyond this is not suggestive The sediment shows a few leukocytes and epithelial cells, but no crystals, and rarely a short motile bacillus The final portion is light in color, clear, and often profuse No detailed chemical or spectroscopic examinations were made

In a few cases, the blood-pressure is high (up to 180 mm) at the outset, and falls progressively with repeated lavage, and shows improvement in the essential symptoms In these cases a trace of albumin and hyaline casts are to be found at the outset, which gradually disappear

Women thirty-five years of age or more form the majority of these patients Men are relatively few It may be that office practice, from which these patients have been drawn, supply the disproportionate number of women

2 The second type of disturbance which has yielded, to me, surprising results with duodenal lavage consists in biliary colic recurring after cholecystectomy Attacks of right-sided pain, which the patient compares to the colic from which he suffered prior to operation, make their appearance from a few months up to five years after operation They have occurred equally in men and women Some of them report mild jaundice after the attacks, a few presented themselves with jaundice Reflex gastric disturbances (distention, eructations of gas, nausea) are frequent The epigastrium is frequently tender, without muscle spasm or rigidity, and the edge of the liver is painful, though not displaced downward Gastric analysis shows a hyperchlorhydria both in the fasting contents and after a meal, in contradistinction to the findings in many gall-bladder cases Duodenal lavage yields a light colored bile, not so-called "B" bile, sometimes containing red blood-cells, and frequently many leukocytes, occurring both singly and in groups A few have shown needle like crystals None has shown what might be regarded as calculi, and no organisms

Lavage is at first repeated three times a week, later twice a week, and later at longer intervals Patients have been discharged to carry out the lavage at home at intervals of two weeks to a month Frequent lavage is essential at the outset to obtain results, as attacks of colic are not always relieved at first, and indeed, at the outset, colic may be provoked by the procedure

The quantity of bile obtained in both groups of cases varies widely—from 65 to 200 c c—much as in other types of cases.

An explanation of these results is largely a matter of conjecture It would seem in the first group that persistent and frequently repeated drainage facilitates the flow of bile, periodically empties the gall-bladder, perhaps increases the quantity of bile and removes toxic material Proof of this is difficult to obtain clinically.

In the second group the relaxation of the sphincter of Oddi and perhaps of the musculature of the common bile-duct plays a part To this is undoubtedly added the reduced resistance to the flow of bile (as Graham has shown), and the stimulation of a greater flow of bile and perhaps of a more dilute bile in which crystals are less easily precipitated

In conclusion, it may be said that without accepting the many deductions which Lyon has made, the method of duodenal lavage, as suggested by him, offers therapeutic possibilities which are perhaps more valuable than the diagnostic phases which seem important to him

CLINIC OF DR DREW LUTEN

BARNES HOSPITAL

ON THE USE OF QUINIDIN IN AURICULAR FIBRILLATION

THE auricles constitute a relatively unimportant part of the man heart The driving power of the circulation is derived m the musculature of the ventricles, and it is only when the ction of these chambers suffers interference that the symptoms mpaired circulation supervene The auricles serve as reser- rs for the returning blood, they transmit the impulses to tricular contraction, and their systole furnishes a small con- bution to ventricular filling, but it is only in these indirect ys that they add to the efficiency of the circulation

Disorders of the auricles *per se* then, have little effect upon circulation Auricular fibrillation is an important condition, wever, because, in the first place it is frequently an indication damage beyond the confines of the auricles and in the second ace, it offers to the ventricles stimuli at a rate much higher an that to which the latter chambers can properly respond us it is that the ventricles in cases of auricular fibrillation, e driven at a fast rate, except in the relatively small number cases in which a-v conduction is impaired at the same time is fast rate shortens the rest period of the ventricles both latively and absolutely, and sooner or later their efficiency ust be impaired in consequence of it The ventricles are de- ived, also, of the additional amount of blood discharged into em by auricular systole, and therefore are not filled so well as ey are when the auricles are contracting Furthermore, the ry irregularity is a source of constant annoyance to some tients and interferes with proper mental and bodily rest

Because of these facts, therefore, it is obvious that the object of therapy in auricular fibrillation should be the restoration of normal mechanism, provided this can be accomplished *without* attendant dangers so great as to outweigh the expected benefit And even though the risk attendant upon the restoration of normal cardiac mechanism might indeed be considerable, yet such risk might well be incurred, provided the result have a certain degree of permanence, and provided also that other measures relatively free from danger are not at hand to control the ill effects of fibrillation

Digitalis, correctly administered, by depressing auriculo-ventricular conduction can be depended on in patients with auricular fibrillation, in the vast majority of cases, to protect the ventricles against the rapid stimuli furnished by the fibrillating auricles In this way it slows the ventricles and maintains the slow rate even though the abnormal auricular mechanism continues Quinidin, on the other hand, in something more than 50 per cent of all cases will do away with the fibrillation and restore normal mechanism to the auricles But it has frequently been stated that there are certain dangers in the administration of quinidin The question of its employment in a patient with auricular fibrillation, therefore, resolves itself into a consideration of the probable benefits and possible dangers in its administration a weighing of the one against the other These benefits and dangers must be weighed also against those that obtain under digitalis therapy

In considering whether to attempt the restoration of normal mechanism with quinidin or to be content with the maintenance of a normal rate under digitalis, in a patient with auricular fibrillation, therefore, the following questions must be disposed of (1) Are auricular contractions and regularity of the ventricles possessed of measurable advantages over the state of fibrillation of the auricles and its consequent irregular contractions of the ventricles, provided the ventricular rate is the same in both cases? (2) If so, is the restoration of normal mechanism with quinidin attended, at the same time, by dangers greater than such as are incurred in the slowing of the ventricles with digitalis?

If such advantages be admitted and such risks be denied, obviously quinidin therapy should be employed, but if risks be admitted and advantages denied, surely there will be no reason for the administration of quinidin Finally, if the end-result of quinidin therapy be found to possess considerable advantages over the end-result of digitalis treatment, but at the same time greater risks be incurred with quinidin, a third question must be answered Are these benefits and the prospect of their attainment great enough to outweigh the greater risks and thus to justify the employment of quinidin? The determination of the question of quinidin therapy, therefore, resolves itself into an examination of its benefits and dangers, and a comparison of these with the benefits and dangers associated with the alternative treatment, *i e*, treatment with digitalis

In order to aid in the solution of the above question certain patients are presented whose cases illustrate some of the benefits as well as some of the dangers in quinidin therapy These cases are fairly typical Usual as well as unusual effects are shown

Case I —A boy eighteen years of age was admitted to Barnes Hospital June 26, 1922 complaining of weakness, dyspnea, and nausea The history was relatively unimportant until the present illness This began six weeks before admission He was unloading oats when he felt his heart suddenly begin to beat very fast He was in bed two weeks on account of this symptom, nausea and vomiting, and restlessness These symptoms continued for the next four weeks, during which time he was incapacitated, but was not continuously in bed On examination there were much enlargement of the liver and conspicuous edema The heart rate was 170 and the electrocardiogram confirmed the diagnosis of auricular fibrillation There were typical signs of mitral stenosis and regurgitation

He received tincture of digitalis in large amounts—17 c.c in two days The rate declined to about 70 and the patient made rapid improvement Five days later (June 31st), after a preliminary test dose, he was given 10 grains of quinidin sulphate

at 9 A M and 10 grains at 12 noon An electrocardiogram at 5 P M showed normal mechanism, rate 92 Subsequent records showed no abnormality The patient was discharged in good condition on August 8th

He returned December 16, 1922, stating that he had been well since discharge and had taken no medicine during the past two months During the night before admission he suddenly felt his heart "jumping," he was dyspneic, and vomited several times When examined it was found that he had auricular fibrillation with a ventricular rate of 208 After a reduction of the rate to 92 under digitalis, he was given two doses of quinidin, 10 grains each, six hours apart, on December 23d The next morning the cardiac mechanism was normal and remained so until his discharge from the hospital on January 3, 1923

He continued to take quinidin in 3-grain doses three times a day until February 6th, at which time he began to take the same amount only every other day He was lifting a half-filled coal bucket on February 11, 1923, when his heart began to thump as before He came to the out-patient clinic, was given quinidin, and the next day when he entered the hospital the mechanism was again normal He remained in the hospital only a few days

On June 30, 1923 he was admitted for the fourth time, with the same symptoms as on previous occasions An electrocardiogram again showed auricular fibrillation, and again, after reduction of the rapid rate with digitalis, he was given quinidin The drug was administered in 10-grain doses every four hours, beginning on July 3d At 3 P M the next day his heart was regular The normal mechanism continued during the remaining few days of his stay During this time he was given 2 grains of quinidin three times a day, and was instructed to continue this after leaving the hospital

On August 14, 1923 he returned again He had taken quinidin as instructed and had felt well until 9 A M of the day of his return At that time his heart suddenly began to beat fast and he felt weak and dyspneic Records showed auricular fibrillation with rapid rate as before, and again, after preliminary digitalization with slowing of the rate, he was given quinidin

The drug was administered as follows first day, 5 grains three times a day, second day, 10 grains three times a day, fourth day, 15 grains twice a day On the fifth day he was nauseated, had ringing in the ears, and objects appeared several times their size The electrocardiogram at this time showed auricular fibrillation, but on awaking the following day the mechanism was normal He was given 5 grains of quinidin three times a day for the next week, and was then discharged with the direction to continue the drug in that dosage

He remained well and was working as a stock clerk when on the night of November 18, 1923 he was awakened with the same symptoms that had been associated before with the onset of auricular fibrillation This condition was verified at the hospital next day, and digitalis was administered The ventricular rate showed some reduction, but was still about 100 per minute when quinidin, 1 gram three times a day, was administered along with digitalis After a few days digitalis was discontinued, the rate being 78, but with an increase in rate digitalis was resumed and quinidin was increased to 5 grains every four hours During the next twenty-four hours he received 3 grains of quinidin every four hours On the following day he received 5 grains of quinidin every four hours for five doses and then 10 grains four times a day After two days of this dosage he was given 10 grains of quinidin every three hours, six doses a day This was continued for two days, after which time quinidin was reduced to 8 grains three times a day, and on the following morning it was found that the cardiac mechanism was normal, with a rate of 72 He continued to receive quinidin 4 grains three times a day for seven days at which time he had an acute sinusitis and auricular fibrillation returned

Larger amounts of quinidin were required to again produce mechanism The drug was administered at intervals of several days in amounts up to 10 grains every four hours without effect For forty-eight hours he received 15 grains every four hours, and under this dosage normal mechanism was again established He was given 10 grains three times a day for the next ten days and then discharged from the hospital

Case II —A woman forty-two years of age was admitted to the hospital March 2, 1923, complaining of weakness, dull pain beneath the costal margin, a sensation of fulness in the stomach, and belching She had had influenza one year before admission and had felt more or less weak since that time, but had been able to do her work as a stenographer until six weeks before admission At that time she had another attack of influenza and following this her symptoms had been increased She had recently been taking "green drops," presumably digitalis

There was no enlargement of the liver and her general condition was good She had been annoyed, however, by the irregular beating of her heart, as well as by the symptoms mentioned above The ventricular rate was reduced from 105 to 70 under digitalis, and then, after a preliminary dose of 2 grains, 5 grains of quinidin was administered at 10 A M , and 10 grains at 2 P M , May 14th The next day she received three doses of 10 grains each, and two such doses on May 16th An electrocardiogram then showed normal mechanism She remained in the hospital four days, during which time no irregularity was noted

On June 6th the heart rhythm was absolutely irregular again Under digitalis the rate was kept within normal limits, and on July 23d quinidin was administered, 10 grains four times a day That night she experienced sensations of faintness, tingling, and giddiness On the next day (July 24th) she received 5 grains every two hours for three doses, and then one dose of 10 grains Following this normal mechanism was established She was seen at rather frequent intervals during the next seven months, and upon every occasion the heart was regular, nor had she had any symptoms which previously had attended fibrillation

Two months later—*i e*, about nine months from the time that the mechanism had become normal—she was seen again She had felt badly and had noticed cardiac irregularity for a few days The rhythm was absolutely irregular After preliminary digitalization she received 5 grains of quinidin every four hours during the day and one dose at night The amount of quinidin was increased to 6 grains every four hours This produced auricular flutter It was then increased to 10 grains every three

hours, and after four such doses normal mechanism was established She experienced the same symptoms while taking quinidin that she had had before

The resumption of auricular fibrillation had always been attended by annoying symptoms, particularly the sensation of irregularity and uneven cardiac action Ten days after the establishment of normal mechanism under quinidin she again noticed these annoying sensations, fibrillation was diagnosed clinically, and normal mechanism was again re-established with 5 grains of quinidin every four hours for about a day and a half She had no further symptoms of fibrillation for seven weeks, but at that time she began to have short periods of irregularity This continued for two months, since which time no effort has been made to restore normal mechanism, but the rate is kept within normal limits with about 22 drops of tincture of digitalis twice a day The patient experiences very little subjective sensation from the irregularity and is in good general condition

Case III —A woman aged sixty-two was admitted March 14, 1923 complaining of intermittent attacks of "heart beating fast and thumping" She had had diphtheria in childhood and a severe attack of grippe at twenty-seven The attacks of which she complained had begun two and a half years before admission She had had two, and then no more for about two years Then for four months they had occurred about every three weeks, but none had been noted for a month previous to admission She usually succeeded in stopping an attack by drinking hot water with pepsin and soda

Upon admission she appeared to be in good general condition There were no evidences of heart disease except that the left border of percussion dulness was slightly increased The patient had no discomfort An electrocardiogram showed mechanism normal, rate 108, and signs of right ventricular preponderance

Several days after admission it was observed at morning rounds that the patient's heart was beating arhythmically There was a soft systolic murmur at the apex She experienced the usual sensations of an "attack" An electrocardiogram showed

auricular fibrillation, rate 170 Hot water, pepsin, and soda were administered several times without effect

At 1 20 P M she was given 2 grains of quinidin as a test dose She was seen at frequent intervals by the intern and no evidences of idiosyncrasy were noted She was accordingly deemed suitable for quinidin therapy, and at 5 30 P M 5 grains of the drug were administered At 6 P M it was noted that she felt better, her "heart not beating so violently," rate 102 At 6 30 P M she felt "like a new woman", the apex and pulse were both 96 and regular

At 6 15 P M she vomited after taking milk At 7 P M it was noted that the skin was cold and moist, and that the patient had had two fluid stools An electrocardiogram showed normal mechanism, the P wave lower than at first, and the T wave negative in Lead I, lower than at first in Lead II At 7 30 P M she was "pale, sweaty, vomiting, pulse weak, diarrhea" The house physicians were genuinely alarmed By 9 P M these untoward symptoms had disappeared and she felt better The next day she felt badly and "ached all over" The heart rate was 84, regular, except for occasional interruption

On the second day following an electrocardiogram revealed auricular fibrillation This was succeeded by normal mechanism on the next day and by fibrillation again a few days later Digitalis was administered meantime, and the rate, when fibrillation recurred, was kept low After a few days she was discharged in good general condition

Case IV —A man aged forty-four was admitted April 23, 1923 complaining of dyspnea, palpitation, and tightness in the chest These symptoms were of two years' duration He had had several attacks of rheumatic fever His general condition appeared to be good There were typical signs of mitral stenosis, the liver was somewhat enlarged, there was no edema An electrocardiogram showed auricular fibrillation The T wave was negative in Lead III, diphasic in Lead I The ventricular rate was 100 The patient had been receiving 15 drops of tincture of digitalis three times a day for a week prior to admission

He received quinidin as follows April 26th, 20 grains, 27th, 20 grains, 29th 36 grains, 30th, 40 grains, May 1st and 2d, 40 grains each day, 3d 4th 5th, and 6th, 70 grains each day, in doses of 10 grains every two hours, 7th, 150 grains (10 grains every hour from 6 to 8 inclusive), 8th, 160 grains (20 grains every two hours), 9th, 20 grains, 16th, 240 grains (30 grains every two hours) There were no symptoms attending any of these excessive amounts of the drug, except that for a short time during the night of the 16th (after 240 grains) he was nauseated and vomited There were no other symptoms, and on the following day he felt quite well Auricular flutter, with a conspicuous slowing of the auricular movements (as low as 150 per minute), followed the administration of some of the larger amounts The patient was discharged after a few days with auricular fibrillation still persisting

Case V—A woman forty-three years of age entered the hospital May 2 1924 complaining of smothering spells and attacks of palpitation Three years previously she had had dropsy for a time and afterward noticed dyspnea on exertion On examination the typical signs of mitral stenosis were noted The heart was absolutely irregular rate 160 The liver extended 3 cm below the costal margin There was considerable dyspnea The electrocardiogram confirmed the diagnosis of auricular fibrillation The T wave was upright in all leads, there were a few left ventricular extrasystoles Her general condition was regarded as "fair" She was kept at rest and on May 4th was given 8 c c of tincture of digitalis in four doses The next day (May 5th) she felt much better, there was much less dyspnea and the ventricular rate was 92 One extrasystole was noted in the electrocardiogram On May 7th, 8th, and 9th she received a total of 8 c c of the tincture of digitalis, 16 c c since admission No more digitalis was administered, the apex rate varied from 60 to 70 and she felt quite well

After a conference it was decided to administer quinidin, and, after a discussion with the patient of its possible benefits and dangers, she consented to its administration Accordingly

at 3 15 P M, May 15th a test dose of 3 grains was given On May 16th she began to receive 5 grains four times a day An electrocardiogram taken at 10 30 A M May 16th was reported as follows "Auricular fibrillation ventricular rate 70, runs of right or left ventricular extrasystoles of varying forms follow each normal beat by approximately equal intervals Question of digitalis effect Question of toxic quinidin effect" A record made at 6 30 P M the same day showed "Runs of coupling, the extrasystoles varying in form and arising in several different foci in the ventricles Question of drug effect"

The next day (May 17th) at 9 A M it was noted that the rate was 46, "and extremely regular" An electrocardiogram two and a half hours after the first dose of quinidin on that day showed no coupling, but later coupling was observed clinically "with a sudden change of rate from 46 to 70"

The patient was seen by the nurse on her rounds at 4 P M, and no unusual symptoms were observed She ate supper as usual At about 6 P M she asked for a drink of water, and as the nurse approached, the patient, who was resting on her elbow, suddenly became cyanotic, her breathing became stertorous, and she fell back, dying instantly

Comment —These 5 cases are reported not with the object of using them in any detailed study of the technic of quinidin administration, but because they afford certain data bearing on the question of the advantages and disadvantages which quinidin therapy possesses over digitalis They will be referred to, therefore, in a brief consideration of the comparative benefits and dangers in the employment of the two drugs

RELATIVE BENEFITS

Rate —Quinidin, successfully employed, restores to the pacemaker its function of determining the rate of the auricle and, consequently, that of the ventricle After this restoration is effected, the control of heart rate is difficult of accomplishment If the sinus rate is too fast, slowing of any considerable degree, in most cases, is then impossible During the persistence of auricular fibrillation, however, ventricular rate can, as a rule, be

maintained within normal limits by digitalis Regarding solely the control of ventricular rate, therefore, in a patient with auricular fibrillation, digitalis is to be preferred over quinidin In those patients, indeed, whose sinus rate when restored might be expected to be fast—*e g*, patients with thyroid intoxication—it would appear that, if the ventricular rate, under digitalis, is slow, the successful employment of quinidin would result in considerable disadvantage to the patient

Auricular Systole —The object of quinidin therapy is to restore to the auricle a normal function—*i e*, the delivery to the ventricle of a certain amount of blood with each auricular systole, thus contributing to ventricular filling and increasing in this way the efficiency of ventricular systole There can surely be no question that this normal function possesses advantage over the state of fibrillation in which auricular systole dose not occur, and that in this respect successful quinidin administration results in an advantage not afforded by digitalis Herein lies the chief claim of quinidin to a place in therapeutic medicine How great is this advantage? How much does auricular systole add to the efficiency of the circulation? Does it add enough to overbalance the greater risks which have also been claimed for quinidin? These questions will be taken up along with a consideration of the relative dangers in quinidin and digitalis therapy Attention, meantime, must be given to another question of relative benefit

Rhythmicity.—Successful quinidin therapy restores to the ventricle the rhythmicity of which auricular fibrillation deprives it This has been enumerated among the advantages accruing to the account of quinidin in a comparison with digitalis It must be admitted that lack of rhythmicity, in so far as it may imply certain periods of tachycardia, will be harmful to the ventricle by calling upon it to work before it has had sufficient rest But it is often overlooked that, along with the ventricular slowing brought about by digitalis in auricular fibrillation, the action of the ventricle becomes more nearly rhythmic. That very action of the drug which produces slowing allows impulses to reach the ventricle only at more nearly equal intervals It is difficult to

understand how mere lack of rhythmicity, provided the interval between beats is not short, may be harmful to the ventricle Digitalis lengthens the interventricular interval, and, as was said, causes this to be more nearly constant Indeed, it is not uncommon for competent clinicians to overlook auricular fibrillation in a patient who has been thoroughly digitalized, so nearly regular may be the ventricular action There would appear to be but little advantage, then, so far as the ventricle is concerned, in substituting rhythmicity for a state which approximates it

The same considerations apply to the unpleasant sensations which irregularity sometimes induces, particularly in nervous individuals The patient in Case II, who was annoyed by the irregular beating of her heart, and who sought relief from the symptom, now suffers very little annoyance from the slight irregularity accompanying the auricular fibrillation, so favorably is it influenced by digitalis

RELATIVE DANGERS

Embolism—It has long been claimed that the resumption of auricular systole might increase the likelihood of loosening parts of a possible auricular thrombus So far as I am aware no extended statistics are available which furnish a comparison between the proportional number of cases of embolism in patients with auricular fibrillation occurring in cases treated with quinidin and in those not so treated *It would certainly appear that* such danger would be enhanced by auricular contractions, and this danger has been emphasized by eminent authorities Cases in which embolism occurred just after the restoration of normal mechanism with quinidin have been reported Until comparative data are available, however, we cannot be positive that quinidin actually does produce a greater proportion of such occurrences than takes place in similar cases in which quinidin is not employed, however much it may seem reasonable to assume that it does

Toxicity.—Almost all drugs are toxic if administered in excessive amounts If toxic symptoms supervene after an amount of

a drug but little in excess of the amount necessary to induce therapeutic effect, the administration of such a drug must be attended by a certain degree of danger Safety in the employment of a drug, therefore, is mainly proportional to the width of the zone between therapeutic effect and toxicity

Another requisite for safety is that the therapeutic dose and the toxic dose be relatively constant for different individuals, in other words, that the borders of the zone between therapeutic and toxic effect be fairly constant between individuals

Judged by both of these standards, quinidin is a much more dangerous drug than digitalis Mild toxic symptoms are common at or before the stage of its desired effect on the auricular mechanism This was observed in Cases I and II How far the drug may be pushed after the appearance of these symptoms is unknown, but the rather large number of reported cases in which, with little forewarning, death has occurred with collapse or with evidences of toxic action upon the heart, leads to the conclusion that this zone of safety is a narrow one Between individuals there is a great variation in dosage Patient in Case III exhibited alarming symptoms after 5 grains of quinidin—a relatively small dose for most patients—although she showed no idiosyncrasy to the drug after the usual test dose of 2 grains The comparison with Case IV is most striking This patient received 98 grains per day for six successive days without symptons, and later he took 240 grains in a single day with only mild symptoms during the following night Such a narrow limit between therapeutic and toxic dosage and such variation between individuals is unknown, so far as I am aware, in the administration of digitalis

Whether or not the death of the patient in Case V was due to quinidin is open to question Sudden death is not uncommon in patients with heart disease, and it is frequently erroneous to conclude "post hoc, ergo propter hoc" Sudden death has been reported as due to quinidin, however, under circumstances not unlike those in this case There are no distinctive signs by which quinidin death can always be surely recognized *This very uncertainty makes for danger*, because in the case of deaths that are due to quinidin the drug may so easily escape blame and

valuable lessons may thus fail to be learned In some measure this is true of digitalis, but not to the same extent The danger signals are better known, and death from digitalis is more likely to be correctly interpreted Dangers that are better understood can be better avoided

It would appear evident, therefore, that the careful administration of quinidin to a patient with auricular fibrillation is attended by a certain amount of danger, and that this danger is greater than in the careful administration of digitalis But while the relative risk is greater, the absolute danger in giving the drug, particularly in selected cases, is doubtless not very great Furthermore, while certain relative advantages are evident, it would appear that these advantages likewise are absolutely rather small Just how much auricular systole contributes to ventricular filling is dependent upon several varying factors, and physiologists are not in agreement as to just how much it adds to the efficiency of the circulation, but even though auricular systole were possessed of an importance much greater than physiologists think probable, it must be remembered that the prospect of achieving it are only about 50 per cent in the average case, and that after it is attained, possession is usually of short duration Whatever dangers exist, therefore, are usually multiplied by reason of these two facts The patient in Case I is a fairly typical example The duration of normal mechanism in this case after each restoration with quinidin was as follows six months, seven weeks, four and a half months, six weeks, two and a half months, one week Even though the dangers may be slight, therefore, they must be incurred with no preponderant probability of benefit and with small probability that they must not soon be incurred again And for what end? For the attainment of a goal which is thought by many investigators to be of only small value when achieved, and whose value by others is regarded as not very great Even so, such an object might well be regarded as worth the seeking were no other less dangerous means available to mitigate the ill effects of the malady

A fair statement, then, of the question of quinidin administration would appear to be as follows Can we, by administering

quinidin to a patient with auricular fibrillation, thus attempting to restore normal cardiac mechanism, reasonably expect to secure to the patient results which are so far advantageous over the favorable effects of digitalis as to outweigh at the same time the greater dangers which the administration of quinidin involves? Only in exceptional cases would it appear that an affirmative answer should be returned Indiscriminate employment of quinidin would only multiply its dangers

CLINIC OF DR ALPHONSE McMAHON

FORMERLY ASSISTANT PHYSICIAN, ST JOHN'S HOSPITAL

MULTIPLE MYELOMA

Classification and Differential Diagnosis Value of *x*-Ray Therapy in Controlling Symptoms Prognostic Signs

THE case for demonstration this afternoon is one which we were fortunate enough to present during his first observation at St John's Hospital At that time a diagnosis of *multiple myeloma* was made, the growths invading practically every bone of the osseous system The elapse of time between the first observation and this presentation confirms our original diagnosis

Myeloma is a rare condition, involving the bone-marrow, chiefly of the ribs, the vertebræ, and the sternum, although diffuse osseous involvement has been reported in many cases The condition is characterized by the growth of multiple tumors derived from the hemapoietic cells of the bone-marrow. The structure is uniform, composed of plasma-cells or their derivatives The tumors are malignant in nature, though in the majority of cases there is no tendency to metastasize Growths arise simultaneously in the various bones involved, gradually replacing the normal marrow, slowly increasing in size, expanding, and then eroding the cortex, growing out into the soft tissue surrounding the bone A variety of symptoms and complications result, depending upon the location of the growths

The term "multiple myeloma" was first used by Von Rustizky in 1873,[1] who described the clinical condition characterized by multiple bone tumors, associated with Bence-Jones protein in the urine This protein, variously termed "proteose," "albumose," etc , had been described by Bence-Jones and McIntyre

in 1848,[2] who discovered it in a case of what was then called *mollities ossium* Although the protein is found in about 80 per cent of the cases of multiple myeloma, its presence is not definitely characteristic of the condition, for it has been reported in several other clinical conditions which chiefly involve the bones

In 1889 Kahler[3] reported a case of eight years' duration and the disease is often called *Kahler's disease* Following the association of Bence-Jones proteinuria with multiple myeloma, cases were reported more frequently Weber[4] in 1903 recorded 28 cases and added 10 cases more Moffatt[5] in 1905 recorded 39 cases Permin[6] in 1907 recorded 40 cases Martini[7] in 1916 recorded 204 cases, adding 1 new case

In presenting this case again, it may be well to review the original case history

Mr W J P, No 4486, aged thirty-two

Present History—The chief complaints on entrance into the hospital January 11, 1924 were (1) *persistent nausea and vomiting, with anorexia,* (2) *cramping colicky pain in the left chest anteriorly,* (3) *pain in the thoracic spine, radiating anteriorly, localizing in the substernal area,* (4) *extreme loss of strength,* (5) *loss of weight,* and (6) *constipation* Duration Sixteen months Course The onset was sudden In September, 1922 the patient was jerked by a roped steer, following which he complained of severe paroxysmal pain in the lower left chest anteriorly, occurring several times a day, lasting about a half-hour The pain was of a cramping colicky character, distinctly aggravated by movement, breathing, and coughing The attacks of pain gradually increased in frequency and severity and in September, 1923 nausea and vomiting appeared These symptoms would occur irrespective of the ingestion of food Owing to weakness the patient was obliged to cease all work and remain in bed The nausea and vomiting have been present practically constantly since their onset, associated with anorexia The thoracic pain has been intensified during the last four months, accompanied by an extreme loss of strength and a gradually progressive loss of weight (exact amount not known) Within the past two

months the pain in the thoracic spine has appeared, being so severe at times that the patient is unable to breathe normally This pain originating at the level of the sixth to the eighth dorsal vertebra, radiates anteriorly in both sides of the chest to the substernal region, where it localizes and attains its greatest intensity. It likewise is aggravated by movement, breathing, and coughing The character of the pain varies being occasionally dull and pressing and at other times sharp shooting, or stabbing, following the course of the intercostal nerves with infrequent radiation to the epigastrium and gall-bladder region The patient has been obliged to take frequent narcotics for relief of the intense pain and when the paroxysm is present he is forced to remain absolutely quiet At the present time he is so exhausted that he is unable to maintain the erect position for any length of time The semirecumbent position seems to give slight relief during the paroxysms, the pain being aggravated when complete recumbency is assumed There is no history of associated pulmonary condition as evidenced by hemoptysis cough or respiratory embarrassment, of headaches vertigo or visual changes, or of gall-bladder or appendical disease

Past History—The patient through life has enjoyed excellent general health, having done heavy manual labor on the farm Usual childhood diseases No history of infectious disease other than influenza in 1921, with normal convalescence and recovery Respiratory system negative Circulatory system negative Gastro-intestinal No history other than nausea vomiting, and anorexia, as mentioned above Appetite always good until the present illness Genito-urinary Occasional dysuria with frequency (formerly twelve to fifteen times daily and two or three times at night) Pollakiuria at this time but no polyuria Nervous system. No motor or sensory disturbances General excitability and nervousness at times No operations, no injuries

Personal History—Sleep not disturbed until the onset of the present condition, since which time he has been unable to rest because of pain Appetite poor Bowels constipated, requiring laxative every night Nycturia occasionally two to three

times Tea and coffee in moderation Alcohol not used Tobacco, cigarettes moderately until the last few months Venereal history negative

Family History—Father living, aged fifty-five, well Mother died at forty-five, hemiplegia Three brothers living, well Two sisters living, well, one recently had an operation for carcinoma of the uterus No family history of tuberculosis, mental disease, or condition similar to that of the patient

Physical Examination.—Well developed, fairly well nourished, showing evidence of loss of subcutaneous tissue Faint subicteric tinge over the entire body, somewhat intensified on the exposed surfaces Sclerae not jaundiced Patient in semi-recumbent position, with the trunk slightly flexed and inclined to the left in an effort to maintain compression in the left chest for relief of the pain Expression anxious in anticipation of pain Mucous membranes show slight pallor, likewise the nails of both hands and feet No gross osseous abnormalities No edema, cyanosis, or dyspnea Temperature, 98° to 99 4° F Regional signs *Head* regular in contour, slight vertical flattening, no bony eminences, tumefactions, tender points, or areas of softening No discolorations of the scalp No pressure tenderness over the sinuses or nerve exits Hair of medium texture, with a diffuse alopecia of slight degree *Ears* negative *Eyes*· Sclerae normal Pupils equal, regular, react promptly to light and accommodation Eye muscles intact, no thyroid signs *Nose* negative *Mouth*· Pallor of mucous membranes of the lips and cheeks, pharynx somewhat injected Tonsils not enlarged Diffuse dental caries, with peridental infection *Neck*· Few enlarged submaxillary lymph-glands, occasional glands palpable in the posterior cervical chains (those in the axillary and epitrochlear regions negative) Small nodule palpated in the right lobe of the thyroid, circumscribed, with no thrill or bruit, no enlargement of the rest of the gland *Chest*· Moderate amount of subcutaneous tissue, with slight degeneration at both bases posteriorly Limitation of motion at the left base Thorax inclined slightly to the left On auscultation, decrease in voice and breath sounds at both bases posteriorly, more marked

at the left Definite tenderness elicited on pressure over the lower left chest anteriorly and in the lower left axilla No points of localized tenderness No enlargement of the ribs in this region *Heart*· Apex impulse at the fifth interspace, within the mammillary line Cardiac sounds negative throughout Pulse, 62 to 80 *Abdomen*· Hyposthenic type, with slight fulness about the umbilicus No tenderness or rigidity on light palpation, no masses palpated *Liver* Lower border palpable on deep inspiration just below the costal margin, not tender *Gall-bladder region* free from tenderness and tumefaction *Spleen* not palpable, some tenderness on pressure over this area, embracing the lower left chest and axilla *Kidneys* negative *Colon* negative *Genitalia* negative *Rectum* negative *Extremities* Bones and joints negative throughout, no localized tenderness, no tumefactions *Vertebral column*· Definite tenderness elicited on pressure over the sixth, seventh, and eighth dorsal spines, most marked at the spine of the sixth Some pain in this area on forced extension or flexion of the trunk *Reflexes*· Normal throughout, no pathologic toe reflexes

Laboratory Examination —*Blood, 1/12/24.* Erythrocytes, 3,400,000, leukocytes, 6800, hemoglobin, 80 per cent Differential polymorphonuclears, 75 per cent , large lymphocytes, 14 per cent , small lymphocytes, 9 per cent , transitionals, 1 per cent , large mononuclears, 1 per cent Stained smear, no abnormal cells *1/19/24* Smear shows occasional basophilic myelocytes, transitionals 3 per cent *2/6/24* Occasional neutrophilic myelocytes, no changes in the erythrocytes Wassermann reaction negative *Urine* (several specimens) Specific gravity, 1 010 to 1 018, faint to medium trace of albumin, microscopic negative, *Bence-Jones protein negative Gastric contents* Free HCl, 70 per cent , combined acidity, 25 per cent , otherwise negative *Feces* negative *Basal metabolism*, +2 per cent

x-Ray Examination —(Radiographic report of Dr J C Peden, St John's Hospital, 1/12/24) *Teeth*· Some pyorrhea, absorption about the roots but no definite evidence of abscess formation, small cavity of the upper left central incisor *Thoracic vertebræ*· In both positions, slight roughening on the articu-

lar surfaces of the vertebræ, especially the twelfth dorsal Very peculiar condition shown also in the ribs and humeri, characterized by numerous small areas of bone absorption of rounded or oblong shape, giving the appearance of a metastatic malignancy *Skull* Complete involvement of all the bones by this peculiar condition consisting of large and small rounded, well-circumscribed areas of bone destruction *Right femur* Evidence of this condition in the femur, small rarefied areas in the proximal ends of the tibia and fibula *Right shoulder* Involvement of the proximal end of the humerus, growths invading the scapula *Pelvis* Entire pelvis involved, including the upper end of both femurs *Hands* No evidence of pathology *Fluoroscopy* of the *chest* and *gastro-intestinal tract* negative

x-Ray diagnosis *Multiple myeloma* (?), *metastatic malignancy* (?)

Progress in the Hospital —When the patient entered the hospital, the pain in the chest and dorsal spine was so severe that narcotics were resorted to in an effort to produce relief This symptom continued, increasing somewhat in severity, and other pains appeared in various parts of the body, severest in the left hip, also present in the lumbar spine Deep *x*-ray therapy was administered in an attempt to alleviate the pain and at the same time a study was made of the effect of the *x*-ray exposure upon the growths Extreme general reaction was experienced following each of the early radiations, with a resultant severe diarrhea, necessitating the discontinuance of the active treatment However, they were resumed at a later date with little or no distress to the patient The treatment seemed to afford some relief from the more acute pain Radiographic examination of the bones, however, revealed no change in the course of the growths The substernal pain continued to increase, with the development of exquisite tenderness in the sternum No crepitations or areas of softening could be palpated At no time did the bony tumefactions reveal themselves externally, although the tenderness in the left chest became more pronounced The nausea and vomiting were the most difficult symptoms to control

Frequent observations of the blood revealed no constant

number of myelocytes, occasional cells being observed in the smear No marked fluctuation in the leukocyte count occurred The erythrocytes showed a gradual tendency to increase in number Bence-Jones protein was never found in the urine, although albumin (a faint to moderate trace) was reported on several occasions The microscopic examinations were always negative

About six weeks after entrance into the hospital, gradual improvement was noted The nausea and vomiting abated and the pain became less severe, the patient gradually regaining his strength, so that on discharge from the hospital on March 19, 1924, he was able to be up and about with some comfort, still complaining, however, of an exaggeration of pain on sudden or unusual movement Aside from the symtomatic treatment, the only medication administered consisted of bichlorid of mercury and iodids by mouth The *x*-ray exposures given were as follows

200 Kilovolts, 5 Milliamperes

Date		Minutes.
1/29/24	Right shoulder	50
1/31/24	Right hip	40
2/ 7/24	Right shoulder	50
2/26/24	Pelvis	30
2/27/24	Pelvis	25
2/28/24	Abdomen	25
2/29/24	Abdomen	25
3/ 1/24	Chest	25
3/ 3/24	Chest	25
3/ 5/24	Hips (posterior)	50
3/ 6/24	Hips (posterior)	50
3/ 7/24	Hips (posterior)	50

The second observation was made the following August. The clinical note at that time is as follows "The patient has been improving gradually since leaving the hospital There has been a return of strength, an increase in appetite, and freedom from all pain except occasional slight pain in the precordial region, occurring usually after exercise He is able to be up and about, rides horseback, and does ordinary light duties" In the interval a marked change had occurred in the patient,

evidenced in the freedom of movements, increase in weight, and definite gain in strength The physical examination at that time revealed no gross changes in the bones, as palpable tumors or areas of softening The tenderness in the lower left chest and axilla had entirely disappeared Slight tenderness was elicited on pressure over the dorsal spines and the sternum No pressure tender points or areas of softening were evidenced in the skull

The radiographic examination showed some changes in the appearance of the growths In the skull there was noted a fusion of some of the original discrete areas, resulting in much larger areas of rarefaction, apparently having eroded both tables of the bone, although this was not confirmed on physical examination The shoulder and knee showed no distinct changes The left foot showed rarefaction in the os calcis The hands revealed a few areas of rarefaction in the first metacarpal bone, but were otherwise negative Involvement of all the ribs was noted, not advanced over the original condition The pelvis showed all bones involved, including the sacrum and lumbar vertebræ

The laboratory examination was as follows *Blood*· Erythrocytes, 4,900,000, leukocytes, 4800, hemoglobin, 85 per cent Stained smear, some poikilocytosis and anisocytosis, no nucleated red cells, no leukocytes *Urine*· Reaction acid, specific gravity, 1 010, faint trace of albumin, sugar negative, Bence-Jones protein negative, microscopic negative

Between observations the patient had remained on oral medication of bichlorid of mercury and iodids, and during the second observation he was given four high voltage *x*-ray treatments, with a reaction characterized by slight nausea, but practically no other symptoms These were as follows

Date.		Minutes
8/25/24	Chest (posterior)	25
8/26/24	Chest (posterior)	25
8/27/24	Hips (posterior)	25
8/28/24	Hips (posterior)	25

At the present time the patient is in an apparently normal physical condition, complaining of no pain or distress and with a

fair degree of physical efficiency There undoubtedly has been a progression in the growth of the bone tumors, although the

Fig 61 —Myeloma Thorax, showing multiple tumors in the ribs

radiographs do not clearly reveal this In Figs 61 to 65 on close inspection one may note the definite erosion of the cortex

Fig 62 —Myeloma Shoulder Tumors in the humerus, acromion, and body of the scapula

of the bone, the advance in growth being more pronounced in the bones of the skull However, with the exception of the left

fibula, in which the growth has involved the cortex, with elevation of the periosteum, there is no manifestation of complete erosion of the cortex

This, of course, is the ultimate picture to be expected, as these growths continue and by a process of erosion gradually penetrate the cortex, involving the periosteum, with the production of pain It is this affection of the periosteum of the ribs and the associated involvement of the intercostal nerves which accounted for the extreme pain at the first observation Follow-

Fig 63 —Myeloma Pelvis Diffuse involvement of the pelvic bones and of the lower lumbar vertebræ

ing the deep therapy there was a gradual improvement, with cessation of the pain, suggesting a retardation in the progress of the growths A remarkable feature in the case is the absence of pathologic fractures with so extensive an osseous involvement It is an occurrence to be expected and greatly feared We feel justified in presenting this case as one of myeloma on the basis of the peculiar circumscribed growths in the medullary portions of the long and flat bones, including the vertebræ and sternum, in the absence of a definite history of malignancy in any portion of the body The clinical course and the present condition of

the patient substantiate this diagnosis It might be well here to present more in detail some of the outstanding features of multiple myeloma

Etiology —The etiology of this condition is obscure About 76 per cent of the cases are males 60 per cent of all cases occurring between the ages of forty and sixty Twenty-six per cent of the cases have been over sixty years of age, while a few cases have been reported in children Trauma, irritation, and infec-

Fig 64 —Myeloma Elbow, showing multiple tumors in the lower humerus and upper third of the radius Knee, showing tumors in the femur and process eroding the cortex of the fibula

tion have been suggested as etiologic factors In a large percentage of cases the factor of trauma has appeared in the clinical history We find this present in our case, the patient dating his entire symptomatology to an injury sustained sixteen months previous to admittance It is very doubtful, however, that trauma plays a distinct part in the production, for in many cases the trauma has been localized to a particular portion of the body, such as may occur in an injury due to a fall, and it is not reasonable to assume that this might account for the simultaneous

appearance of these tumor growths in various and widely separated portions of the body That localized trauma could in some

Fig 65 —Myeloma Radiograms of the skull, (*A*) first observation and (*B*) second observation nine months later The tumor areas in *B* show fusion and are less distinct and clear-cut than in *A* At the vertex there is apparent erosion of the outer table of the skull

way lower the tissue resistance of an individual, allowing the cells to grow in an abnormal fashion, might be assumed if the growth remained localized in the bone at the site of the trauma

That this is not true, however, may be determined by consulting the case histories, wherein we find that the tumors tend to originate in the flat bones (sternum vetebræ ribs, and skull) and only later appear in the long bones, irrespective of the site of the injury The involvement is too diffuse to be explained by trauma as the sole basis

Irritation, such as may occur following drainage of an abscess cavity, particularly about the chest, has also been suggested as an etiologic factor We are not personally able to confirm this Infection may play a more predominant part than we are inclined to attribute to it at this time The simultaneity of the growths, the occasional febrile course, the cachexia, and the history of focal infections existing in many cases for years preceding the onset, indicate that this is a more probable factor Yet our information on the subject aside from clinical reports citing the history of prolonged focal infection, is very indefinite Branham and Lewis[8] cite a case with numerous apical abscesses of the teeth and a generalized oral sepsis developing multiple myeloma about eleven yeras after the first appearance of the abscesses Wood and Lucké[9] report a pyorrhea alveolaris in their case The same condition of fairly long duration, was found in our case The relation of focal infections to the leukemias has been frequently observed It is not illogic to assume the relation of infection also to myeloma, which bears a strong resemblance to the former Both are disturbances of the lymphatic hemapoietic system, the leukemias producing maximum changes in the blood-picture, with minimum hyperplastic changes, while myeloma produces the opposite picture of maximum hyperplastic changes with minimum changes in the blood

The gross appearance of the tumors varies with the age of the tumor and the degree of vascularity The color may be gray, grayish red, or yellowish red There is nothing distinctly characteristic macroscopically, as the tumors may be discrete and isolated, or as in the more advanced cases, confluent and diffuse There is a distinct tendency for the growth to invade the cortex of the bone, resulting in complete destruction and involvement of the surrounding tissues While the chief sites

are said to be the ribs, sternum, and vertebræ, all the bones of the body may be invaded Metastases occur very infrequently The tumors vary from the size of a pin-head to that of an orange Where erosion occurs it may be detected clinically by the distinct thinning of the cortex at the site, evident on palpation, with the production of a crackling sensation Rupture of the cortex is easily effected where the growth is extensive Following the cortex invasion, secondary pathologic features become manifest, such as multiple fractures, cerebral pressure signs, extreme kyphosis or lordosis, collapse of the thoracic cavity, and destruction of the large joints Microscopically, the tumors present definite cell characteristics which classify them as originating from the bone-marrow The tumor occupies a position midway between the leukemias (lymphatic and myeloid) and the malignancies (lymphosarcoma, leukosarcoma, and chloromyelosarcoma) For convenience in classification, myelomas have been divided into four distinct types[10] (1) Plasmocytoma, (2) myeloblastoma, (3) erythroblastoma, and (4) lymphocytoma The origin of the cell in myeloma has not been definitely determined Of the above four types the one most commonly reported is the plasmocytoma, composed chiefly of plasma-cells, rounded, polyhedral, or oval, with an eccentrically placed nucleus containing chromatin arranged peripherally, surrounded by a clear zone and an amphophilic cytoplasm It has been maintained that the characteristic cell of myeloma is a myeloblast derived from the true bone-marrow cells The oxydase reaction does not always serve to differentiate this cell from the so-called plasma-cell In some tumors a cell of the myeloid type containing hemoglobin has been reported,[11] while in others the lymphocyte has been a predominant cell In the few cases reported showing apparent metastases the cell type has resembled the parent cell in the bone-marrow From the literature it seems to be rather doubtful that individual cell types may be maintained for these apparently different tumors Many authorities have suggested that all cells are simply anaplastic forms of the same original cell Morse,[12] in a study of 3 cases of multiple myeloma, discusses the histogenesis of these

tumors He presents data to support his theory that the "plasma-cell myelomata spring from a series of cells whose specific function is bone absorption," and that the "myeloma cell may be a heteroplastic osteoblast" That the tumor cells show a distinct tendency to bone absorption is well known and this fact serves as a diagnostic point In the rarer types of diffuse, confluent medullary involvement, this tendency is not so pronounced as in the commoner types

In the blood we find evidence of a secondary anemia, which is a fairly constant accompaniment of this condition, with changes in the size and shape of the red cells and occasional nucleated forms The erythrocyte count varies, bearing no constant relation to the distribution of the growths or the number of bones involved The reduction in the cell count bears some relation, however, to the duration and progress of the disease In the present case, with very extensive osseous involvement, the erythrocytes did not drop below 3,400,000 per cubic millimeter The leukocytes are seldom increased A few cases have been reported with the count above 10,000 per cubic millimeter In the rather rare type of transitional case consisting of myeloma occurring in conjunction with myeloid leukemia a high leukocyte count is found with the myelocytosis There are no characteristic changes in the differential count The myelocytes vary from 3 to 7 per cent, while in an occasional case they may reach as high as 21 per cent of the leukocyte count Tumor cells have been reported in the blood [13] These are chiefly of the plasma-cell variety In general, the blood changes are those which may be found with any malignancy and, clinically, the associated cachexia confirms this idea of the malignant nature of these growths It may be said that the blood changes, while not definitely diagnostic, in conjunction with the *x*-ray signs of multiple osseous tumor formation render the diagnosis of myeloma more positive

The outstanding symptom in this condition is pain, either localized or referred, depending upon the location and extent of the osseous involvement The character of the pain in myeloma is in itself sometimes sufficient to establish a diagnosis It is,

as a rule, severe and persistent It may be constant or intermittent, superficial or deep-seated, aggravated by motion, and is frequently worse at night It is sometimes uncontrollable, rendering the patient helpless during the exacerbations It may be boring, stabbing, or shooting in character, with peripheral radiation to the termination of the nerve filaments It is associated with a tenderness at the site of the growth, due to periosteal involvement or involvement of the adjacent nerve-fibers With vertebral growths and encroachments upon the posterior nerve roots, the pain is referred to the areas supplied by these affected nerves It is not unusual with involvement of the ribs to find pain referred to the gall-bladder region, epigastrium, or even appendical region Its character usually distinguishes it from pain due to affection in these particular regions Growths in the cranial bones may give rise to a variety of symptoms, depending upon the extent of the growth and the involvement of the underlying cortical substance Signs of focal cerebral irritation may be present and in one case reported by Branham and Lewis[8] there was a close resemblance to the clinical picture of brain tumor, with a unilateral exophthalmos Encroachment upon the spinal cord produces the various symptoms associated with spinal cord irritation and may result in transverse myelitis, with spastic paraplegia It is to be noted that in the case cited above the pain presented all the characteristics of that seen in other cases There was, however, no nocturnal aggravation, as has been described by some authors [14] Other symptoms of less severity are associated with the general cachexia, as loss of energy, loss of weight, and nervousness

Bence-Jones protein appears in the urine in about 80 per cent of the reported cases The consensus of opinion seems to be that the protein is of endogenous origin, probably derived from the blood-proteins, chiefly the globulins, through the enzymotic action of the abnormal cells of the bone tumors It was first described by Bence-Jones in 1847 and termed an "albumose" It has been isolated from the urine, from bone tumors, and from the blood of patients with multiple myeloma [15] In other clinical conditions the same protein has been found present, chiefly in

those associated with bone involvement such as chloroma, tuberculous osteo-arthritis secondary carcinoma and sarcoma, osteomalacia, bone injury, and lymphatic leukemia It is also reported present in myxedema and pleural effusions The essential characteristic in the laboratory test is its tendency to precipitate from the urine at about 55° C The precipitation is complete at 65° C, and 80° C the precipitate is dissolved, appearing when the solution is cooled The subject is discussed most thoroughly by Rosenbloom,[16] who has also reviewed well the literature pertaining thereto It is unnecessary to go into much detail as to the origin of and the experimental work done upon this protein It may be present in the urine in various amounts, bearing no constant relation to the number of growths Jacobson[15] reports a case having a proteinuria of 0 70 per cent (Esbach) The protein was isolated also from the blood, the estimation being 7 86 per cent In conjunction with the Bence-Jones protein, albuminuria is frequently present, with a low-grade nephritis very constantly associated, showing casts of various types in the urine The frequency of the association of myeloma with nephritis suggests the possibility of a relation between the two, according to Wallgren [17]

The radiographs of the bones in myeloma are characterized by multiple tumor formation, usually discrete sharply defined, originating in the bone-marrow and showing gradual involvement of the cortex by lacunar absorption The areas of rarefaction vary in size and tend to coalesce The appearance of the rarefied areas is not characteristic of the condition, differentiation from the secondary metastatic malignancies being difficult Assmann[18] states that myeloma defects are better described than metastatic growths, although it is sometimes impossible to differentiate them Isaak[19] states that it is impossible to differentiate myeloma from secondary tumor, but that the early metastatic growths are less extensive and somewhat more diffuse in character and more likely to be located near the nutrient artery In *osteomalacia* there is no cranial bone involvement The absorption of calcium salts is more diffuse and associated clinically with changes in shape of

the bones The radiographic signs of *lymphosarcoma*, as may be seen from Figs 66 and 67, are similar to those in myeloma, except that these metastases are more irregular, with less of the "punched-out" appearance of myelomatous tumor The primary origin of the growth, with a tendency to metastasis, and the general clinical features serve to differentiate this condition from simple multiple myeloma *Primary carcinoma* is never found in bone, so the exclusion of a primary growth about the body is of valuable assistance in reaching a diagnosis in multiple bone tumors

Fig 66—Lymphosarcoma Thorax, showing in *A* mediastinal gland involvement before deep *x*-ray therapy, in *B* condition after two months' *x*-ray treatment

Myeloma must be differentiated from other osseous involvements, as chloroma, bone cysts, endochondroma, osteomalacia, and myeloid sarcoma *Chloroma* cannot be differentiated from myeloma on the basis of the cell type alone The tumor tends to assume a greenish, iridescent appearance Metastases are frequent and there is usually associated a leukemic condition of the lymphoid or myeloid variety The age incidence also is of assistance in the differentiation, chloroma occurring most frequently in the earlier ages *Bone cysts* oftenest involve the ends of the long bones, showing areas of rarefaction, with fairly well-defined bony outlines In *endochondroma* the areas of rarefaction show

linear striations extending from the epiphyseal lines into the shafts of the long bones *Myeloid sarcoma* seldom involves the ribs and vertebræ, usually being localized at the ends of the long bones, with new bone formation

Treatment —Unfortunately there is little to offer in the way of treatment for these cases In the case described high voltage *x*-ray therapy seems to have produced results, at least as far as the symptom of pain is concerned The patient at the present time is practically free from pain and there has been no marked

Fig 67 —Lymphosarcoma Skull, showing metastases of the malignancy two months after the institution of deep *x*-ray therapy Note the irregularity in outline of the metastases as compared with the clear, "punched-out" appearance of the growths in Fig 65, *A*

tendency to progression of the growths The prognosis in these cases is fatal and any treatment only palliative It may be well to stress again the significance of the duration of the disease as a diagnostic feature The relatively slow rate of progression of the growths and the development of the secondary constitutional symptoms may be of value in differentiating this condition from the primary malignancies with metastases in the bones

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PROGNOSIS AND TREATMENT OF HYPERTENSIVE CARDIOVASCULAR RENAL DISEASE

By hypertensive cardiovascular renal disease we understand organic lesions of heart, arteries, and kidneys, resulting either primarily from essential arterial hypertension or from an antecedent nephritis

As to the etiology of hypertension, this we have considered in a paper entitled The Rôle of Vasomotor Response in Cardiac and Renal Decompensation of Hypertensive Cardiovascular Renal Disease [1] while the disastrous effects of high blood-pressure on heart arteries and kidneys have been depicted in a contribution to the International Clinics [2] The diagnosis of arterial hypertension is, of course, readily made through the aid of the sphygmomanometer The prognosis, however requires much more thought and judgment

In order though, to have a comprehensive appreciation of this phase of the subject, we must recall certain salient points, namely that the causes of arterial hypertension and of a large proportion of cases of arteriosclerosis are as follows First the accumulation in the blood of certain substances called pressor substances and which produce a vasoconstriction of the arterial tree Second, that narrowing of the lumen of the arterial tree, resulting from this vasoconstriction ahead of a pump continuing to pump with a normal force will, according to physical laws, increase the head or arterial pressure Third, the ultimate effect of the strain of the increased head or arterial pressure, is to lead to lesions of the intima of the arteries which calls for reinforcement of the middle and outer coats of the vessels, or, in a word, to arteriosclerosis

The disastrous effects of heightened arterial pressure do not, however, stop here, for the left ventricle of the heart having to pump blood against this increased blood-pressure or peripheral resistance undergoes hypertrophy and, finally, just as in valvular disease of the organ, fatigue of the ventricular muscles from chronic myocarditis ensues Dilatation comes to predominate more and more over hypertrophy, cardiac insufficiency follows, and the victim succumbs with all the distressing symptoms of chronic cardiac decompensation A certain proportion of these cases, however, meet sudden death through sudden stoppage of the heart without the syndrome of chronic cardiac decompensation having developed This group we have described under title Acute Intermittent Cardiac Decompensation [3]

Another group of these cases develop fatal cerebral hemorrhage resulting from the strain of the arterial hypertension on the cerebral vessels weakened through arteriosclerosis Still another group develop fatal uremia resulting from the consequent sclerotic nephritis Moreover, in a final group sclerosis of the coronary arteries may ensue, ending in death from angina pectoris

These, then, are the main end-results of, at the outset, so-called "simple benign arterial hypertension," and how difficult of comprehension does the attitude of those appear who contend that the importance of this subject of arterial hypertension is grossly exaggerated, that high blood-pressure is compensatory and therefore conservative, and hence any effort to reduce this fortunate benign condition must necessarily be fraught with dire results to heart, arteries, and kidneys But we believe we have been able to show in the above-mentioned contributions, through sufficient clinical evidence, that arterial hypertension is neither compensatory or conservative, but on the contrary always destructive sooner or later to heart, arteries, and kidneys

Several prominent authorities also entertain similar views on this subject H A Christian[4] states "If hypertension persists, sooner or later one is able to demonstrate that changes will occur in the larger vessels, arteriosclerosis, that the heart will hypertrophy and heart failure ensue, myocarditis, that renal insufficiency will appear, chronic nephritis"

Moschkowitz[5] says "Many facts tend to show that hypertension should be considered perhaps the most important factor in the production of arteriosclerosis It seems that here, too, the renal lesions may be the results rather than the causes of hypertension, or rather the results of the same disorder causing the hypertension"

Clifford Allbutt[6] states "that high pressure and friction are competent to set up arteriosclerosis was clearly shown by Roy and Adami, and I have adduced familiar proof of it by the alteration of the arterial wall at critical points, as at bifurcations, at narrows, normal or morbid, and again at dilatations, with changes of wave leading to distention and elongation", and again, "vessels which are incessantly subjected to hydrostatic stresses cannot but betray their effects etc, but by arteriosclerosis of high pressure, properly so-called, we mean surely lesions primarily and mainly thus produced in vessels previously sound"

Wiggers[7] says "This vasoconstrictor mechanism is always tonically active, that is, the vessels are always contracted, as may be demonstrated by the fact that when any large nerve, like the splanchnic, is cut, a dilatation of the arterioles with a consequent decrease in the blood-pressure results This activity does not, however, induce a maximal degree of contraction in the muscle fibers of the arterioles, for when such a nerve is stimulated a pronounced additional constriction takes place, with a consequent increase of arterial pressure due to increase resistance"

Again "If in an artificial circulation machine, the peripheral resistance be increased, both systolic and diastolic pressures progressively increase"

Preble[8] suggests that the principle that is most likely to be useful in the management of this disorder (hypertension) is to regard vascular hypertension in this group of cases as the symptom of an intoxication, the nature of which we do not understand

It would seem, therefore, clear that the first step in the development of arterial hypertension is the stimulation of the vasoconstrictor system of nerves by certain substances accumulating in the blood, and called therefore vasoconstrictor or pressor substances Second, that the strain on the arteries by this hyper-

tension leads to arteriosclerosis, that the same strain on the heart results in chronic myocarditis, and the extension of the sclerotic process along the renal vessels develops sclerotic nephritis How can a condition causing such dire results be ever considered compensatory and conservative, and why should we still hear of the importance and seriousness of arterial hypertension as being greatly exaggerated? Simply because some few exceptional cases, fortunately endowed by nature with an unusually sound vascular apparatus, may withstand for a longer period the terrific strain of greatly heightened blood-pressure? or that blood-pressure must not be lowered for fear of possibly inducing a fatal cardiac or renal insufficiency, or because still others would even warn you against taking a patient's blood-pressure, lest you cause him mental anguish should he learn that the reading be high? Certainly, it can hardly appear rational to anyone that the majority should be assigned without assistance to a malady controllable in its early stages, but ultimately so fatal, if not treated, because the exceptional individual may withstand the disease for a few years longer

What intelligent observer, however, has ever seen serious cardiac or renal decompensation induced in compensated cases, or increased in decompensated ones through a rational lessening of blood-pressure? While, on the other hand, every experienced clinician must have witnessed improvement in cardiac and renal decompensation with the removal, through free diuresis of pressure substances from blood, and the consequent lowering of blood-pressure and of the high peripheral resistance ahead of a laboring struggling heart, and in our article in the International Clinics, we have presented groups of cases carefully observed in our medical clinic at Barnes Hospital and in private practice, substantiating the above statements

And as to the third position, we might as well say we must not tell the diabetic he has sugar in his urine, though such knowledge might enable him to give us his co-operation, so necessary to the control of his ailment, simply because he might be disturbed by thus having a sword of Damocles suspended over his head

There is, in fact, only one stage in the malady under consider-

ation in which efforts at lowering of blood-pressure are not only entirely useless but possibly if persisted in may cause harm through being depressing in nature to the contractile forces of the heart, and this is in the later stages of neglected cases, where as the result of the long-continued strain on the arterial tree of persistent high blood-pressure, the walls of this arterial tree have lost their elasticity or vasomotor response from extensive sclerosis or calcareous degeneration The walls of the arteries can then no longer respond to vasodilating influences We have therefore, a set of tubes rigid and fixed at a narrowed caliber with a heightened blood-pressure which cannot be made to fall until the onset of progressive cardiac decompensation ensues this latter condition being at this stage of the disease not far in the distance, for such a fixation of the arterial tree robs the heart of that great assistance in the circulation resulting from the elastic recoil of the aorta and its tributaries during the diastole when, according to Howell,[9] "almost as much blood is propelled forward as during the ventricular systole" At this late stage of the disease also nothing remains to be done except to try to keep the contractile forces of the heart maintained as best we may

It may also be observed that arteriosclerosis cannot be due to hypertension because the condition sometimes obtains with hypotension It is, of course, true that hypertension may not be the sole cause of arteriosclerosis, for when we have the condition thus associated with hypotension, the vascular degenerative changes are here due to senile retrograde processes and therefore the group has been styled the senile or involutionary type of arteriosclerosis, and is quite rare, therefore the group resulting from hypertension still remains the more frequent and important type

If, therefore, as has been heretofore suggested the principle that is most likely to be useful in the management of the disorder in question, is to regard the hypertension as resulting from the presence in the blood of certain toxic or pressure substances causing vasoconstriction, arteriosclerosis, myocarditis, sclerotic nephritis, thoracic aneurysm, angina pectoris and cerebral

hemorrhage, etc, what should be the prognosis, prophylaxis, and treatment of such a formidable malady? Should the patient be kept in blissful ignorance of the earthquake under him, and given absent treatment by his physician, or should not a rational effort be made to stem such a disastrous tide?

From all that has been said it would seem that the prognosis in this class of cases is absolutely dependent on at how early a date the disease can be recognized and an intelligent prophylaxis instituted for the protection and salvation of the cardiovascular renal system Hence, the urgent need of routine blood-pressure observations, especially at or about middle life The insurance companies have contributed much valuable aid in calling to our attention at an early period many of these cases, and they thus teach us all engaged in Internal Medical Work a most salutary lesson When, therefore, at or about middle life a hypertension of 160 or over is detected how is it to be appreciated and handled?

The above question involves a consideration and comprehension of all the known or supposedly known causes of arterial hypertension and their possible elimination, control, or amelioration, and then at the outset, from the standpoint of prognosis, prophylaxis, and treatment should the subject of the affection under consideration be divided into two main classes

First, into the renal and non-renal groups, the former comprising the cases in which the disease has developed secondary to a primary nephritis, while in the latter group, sclerotic nephritis, when present, has developed secondarily to the arteriosclerotic process, the primary cause having been the accumulation of pressure substances in the blood This latter is, by far, the larger group and constitutes the so-called essential hypertension or hyperpiesis of Clifford Allbutt

Second, those still retaining, and those having lost their vasomotor response For, in the first class, the serious and oftentimes fatal results may be altogether prevented or greatly retarded, while in the second group life expectancy is short at best, and the main reliance must be on the maintaining of the integrity of the propelling force of the heart

In the renal type we have, of course, the history of pre-existing

renal disease and evidence of marked renal insufficiency in the low phenolsulphonephthalein test, and in nitrogenous retention in the blood as shown by the high non-protein blood nitrogen findings Here, of course, the prognosis depends, first, on the character and grade of the nephritis and the secondary effects of the hypertension on the heart, and the arteries The treatment also must be addressed to the existing nephritis through a low-protein diet largely of the Karrell type, especially when the blood nitrogen be high, a salt-free diet when edema is present, and to elimination through the compensatory organs of the kidneys, viz the bowel and skin, and through such attention to complications as appears indicated

But we are now most concerned with essential hypertension, not resulting from a primary nephritis, though many points in treatment considered in this latter type may be appropriately applied to the former class In the class of so-called essential hypertension, it is most necessary to look into the several possible causes of hypertension As this condition is most frequently found in the man of affairs, we should first consider the possible sources of wear and tear See how much he is using his head more than his muscles in burning the candle at both ends It is the high tension at which many of this class are living that brings about the high blood-pressure Such individuals must be brought down from first into second speed, be changed for instance from the president of the bank or corporation to chairman of the board, etc These individuals must also be made to realize that they must conserve their energies for matters of pure policy and be relieved of all wearing details They must also spend several afternoons away from their desks on golf links or in the taking of systematic walks, etc , if physically able

Foci of infection as sources of hypertension must also be carefully searched for, as tonsillitis, and if tonsils appear as suspicious foci, they should be removed and my colleague Sluder says "There is only one way to be sure that a tonsil is not a focus of infection, and that is to remove it", and I have come to feel he is not far from right.

Nasal sinuses should also be searched, and in this connection

we must remember that the patient may have sinus disease without being conscious of the existence of such a condition, as my nose and throat friends have frequently found nasal sinus disease in my cases when no symptoms of nasal disease could be elicited

Films of all teeth should be obtained and carefully and competently interpreted, and any found infected should be extracted

Infected appendices and gall-bladders should be removed and all infections of the genito-urinary apparatus should be given proper attention, in both sexes

The intoxications must be considered, as alcohol, tobacco, coffee, tea, and certain poisons of the industries, as lead, mercury, zinc, etc In regard to the relation of these to the production of hypertension we are persuaded that coffee, tea, and tobacco do tend to increase blood-pressure, but that alcohol does not, and that the individual past middle life who has been accustomed to moderate indulgence in alcohol really needs the stimulus, provided, of course, there be no severe grade of nephritis as a contraindication

Auto-intoxication from the digestive tract, we also believe, plays a definite etiologic rôle in quite a number of cases, and in this group it is our custom to eliminate thoroughly, not only through the bowel but also through the portal circuit, giving the patient in the morning a saline, preferably magnesium sulphate, ½ to 1 oz , in ½ glass of water (after the Hay method), which acts during the day And the same night administer a chologogue purge in the way of 2 to 3 or 4 compound cathartic pills, or 5 gr blue mass, or 2 to 5 gr calomel, anyone of which will act the next day, when no more purgative is given until the following day, in other words, every other day the patient receives in the morning a saline, and the same evening a chologogue purge This is kept up as long as apparently indicated, watching, of course, for any suggestion of salivation Lactose also acts well by changing character of intestinal flora

Metabolic and endocrine influences must also be looked for in arterial hypertension Cases of obesity, gout, and diabetes mellitus are often associated with hypertension The basal metabolic rate varies in these cases, some being high, some low,

and others normal A reduction régime in obesity frequently tends to reduce and control the hypertension A H Terry[10] says "On a high protein, low caloric diet there is a lessening of weight, with a lowering of blood-pressure" And here Preble, the editor, interjects the statement "That this is another illustration of the fact that, 'The waist line is the life line'"

In diabetes mellitus, rendering the patient partially or totally sugar-free seems, also to exert a favorable influence on high blood-pressure Fortunately, in arterial hypertension, accompanying diabetes, we are rarely faced with the combination of hyperglycemia and high blood nitrogen, but even in the occasional case in which this blood finding may occur, the diet should be arranged along diabetic rather than hypertensive lines, unless grave uremic symptoms appear threatening

In the last few years we have found not a few references in the literature to association of arterial hypertension with certain endocrine conditions Ever since the days of Addison, who, in fact, first called attention to the condition of hypotension resulting from failure of the secretion of the adrenals, has this subject been accorded more or less space in the literature, but especially during the past few years, and in a comparatively recent contribution by my colleague Engelbach[11] a group of 500 endocrine cases studied by him personally were found to run a systolic pressure of 160 or over He, however, adds this comment "Just what relation diseases of the ductless glands bear to these types of hypertension just enumerated cannot be determined"

L F Baker[12] states "Endocrine disorders are common enough among hypersensitives, but what the relations of these disorders of the thyroid, hypophysis, suprarenals, and gonads, are to hypertension, if there be any, remains to be determined"

It would seem to us that this subject when boiled down results in only the possible casual relation of the thyroid and female gonads to arterial hypertension For many years the thyroid has been thought to be an antagonistic hormone to epinephrin, and more recently Plummer has noted incidence of hypertension

in thyroidism So, in cases of definite deficiency in the secretion of this gland, administration of thyroid substance may exert a possible influence on hypertension Riesman[13] and Hopkins,[14] however, have shown a somewhat more definite relation of hypertension to the menopause and the administration of 5 gr corpus luteum, or better, of the whole gland, does seem to exert a controlling influence on high blood-pressure in these conditions

Allen has called attention to the relation of chlorid of sodium retention to arterial hypertension and urged a salt-free diet in its control We must say, however, that we have not found our blood chlorid readings uniformly high in the majority of our cases

And now, in conclusion, let us consider briefly one or two of the important complications of the affection, such as cerebral hemorrhage, angina pectoris, and the terminal states of cardiac decompensation and uremia It is probably in the first two conditions that the remedies of the vasodilator class find their main indication in this disease Whenever the arterial pressure is running high, with threatening head symptoms, such as severe headache, vertigo, possibly disturbed mentality, then the vasodilators are urgently called for, and should be freely administered until a definite fall in blood-pressure results, with the hope of preventing actual cerebral hemorrhage, and should this complication result, they should be continued to limit the extent of brain damage This class of drugs embraces, first, nitrite of amyl, second, nitroglycerin, third, nitrite of sodium, fourth, erythrol tetranitrate, and fifth, benzyl benzoate It is well to remember that the effects of the first two are very evanescent and must be repeated at short intervals The effect of the third, in doses of 1 to 5 gr (preferably the larger), lasts about two hours, while the effect of the fourth, in doses of $\frac{1}{4}$ to $\frac{3}{4}$ or 1 gr in tablet form, continues for three to four hours, and benzyl benzoate, 30 gtt , three or four times daily of 20 per cent sol also controls blood-pressure for about three or four hours In bad cases of angina pectoris the nitrites should be also used freely in the same way, together with the important aids of morphin and atropin

In uremic convulsions or coma, we resort to free venesection at least 16 oz replacing same amount, with an equal quantity of normal saline solution, or with 10 per cent glucose solution, if any element of acidosis be present, together with insulin if indicated

In the terminal stages of this disease, when the clinical picture approaches that of chronic cardiac decompensation from valvular cardiac affections, we have found a few procedures of value Should the symptoms be not too urgent or critical, then placing of the patient at absolute rest on a strict Karrell diet, 800 c c of milk in twenty-four hours for a week, nothing else, not even water, will often result in a marked diuresis reduction of edema and improvement in dyspnea

In more urgent cases a massive dose of digitalis (½ to 1 min of a reliable tincture for every pound of body weight), so that within twenty-four hours the patient receives from 1 to 2, 3, or 4 drams or more of a reliable tincture, which often produces a marked diuresis and a magical improvement in all of the symptoms Care must be exercised, however, that the patient has not recently had digitalis, as otherwise the effect might be too great or even fatal, then an electrocardiographic tracing is in this connection most important

The third procedure we have found of great value has been the use of the so-called theobromin group of diuretics, which includes in the chronologic order of their appearance in the therapeutic field, first, diuretin in 10- to 20-gr doses, agurin in 10- to 20-gr doses, given in ½ oz of peppermint water, three or four times daily, theocin and theolactin in 5-gr doses in capsules three or four times daily Of these we consider agurin possibly the most reliable, while theocin is the most powerful diuretic of the group, but is least well borne by the stomach Theolactin, although the last given us, is probably the least satisfactory But diuretin, agurin, and theocin are all wonderful diuretics, while seemingly at the same time acting as cardiac stimulants, and often producing marvelous results in apparently desperate situations

The Nauheim or Schott baths and resistant movements also

act well in selected cases, but should be carefully administered with faithful attention to all important details, the consideration of which, however, must be left to monographs on this subject

In conclusion the following deductions naturally follow

I The prognosis and treatment of hypertensive cardiovascular renal disease depends on the period, in the course of the malady, the arterial hypertension is discovered

II If detected before the resulting arteriosclerosis has deprived the arterial tree of its elasticity or vasomotor response, then the prognosis is favorable in so far as the causes of the vasoconstriction or the so-called pressure substances are removable, permitting of a return by vasodilation of the blood-pressure within normal limits, and thereby a conservation or restoration of the functions of heart, arteries, and kidneys While the treatment at this stage will naturally consist in efforts at removal of the vasoconstricting influences, together with agencies addressed to the removal of cardiac and renal decompensation when present

III If appreciated only after the arteriosclerotic process, consequent on arterial hypertension, has resulted in a fixed nonmobile arterial tree, then lowering of blood-pressure by vasodilation is no longer possible, and the prognosis then depends very largely on the ability of the cardiac musculature to withstand the terrific strain of the irreducible arterial hypertension, and treatment at this stage must necessarily confine itself almost exclusively to those measures capable of maintaining for a shorter or longer period of time cardiac and renal compensation, or of relieving, probably only temporarily, cardiac and renal decompensation

IV The prognosis in hypertensive cardiovascular renal disease is also affected by any of the resulting complications to which, of course, appropriate remedies must also be addressed

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